THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY
CHENNAI – TAMILNADU.

DISSERTATION
ON

A STUDY OF CLINICAL, BACTERIOLOGICAL AND RADIOLOGICAL PATTERN OF PULMONARY TUBERCULOSIS AMONG HIV SEROPOSITIVE INDIVIDUALS IN THANJAVUR MEDICAL COLLEGE

SUBMITTED FOR M.D. DEGREE EXAMINATION
BRANCH I
(GENERAL MEDICINE)

EXAMINATION
IN
SEPTEMBER – 2006

THANJAVUR MEDICAL COLLEGE
THANJAVUR

CERTIFICATE

This is to certify that this Dissertation entitled, **"A STUDY OF CLINICAL, BACTERIOLOGICAL AND RADIOLOGICAL PATTERN OF PULMONARY TUBERCULOSIS AMONG HIV SEROPOSITIVE INDIVIDUALS IN THANJAVUR MEDICAL COLLEGE"** is the bonafide record work done by **Dr. A. Mohamed Rafic Babu,** submitted as partial fulfillment for the requirements of M.D. Degree Examinations

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ACKNOWLEDGEMENT

I am extremely thankful to our beloved former Dean Dr. **K. Kalai Selvi M.D.,** and present Dean, **Dr. S. Balakrishnan M.D.,** Thanjavur Medical College, for having granted me permission to do this dissertation in Thanjavur Medical college hospital, Thanjavur.

I am grateful to our Professor and Head of the Department of Medicine, **Dr. K. Gandhi M.D.,** for his acceptance to do this dissertation and his guidance during the study.

I thank **my unit chief Dr. S. Ramasamy M.D.,** for his colossal suggestions, assortment of emerging views and constructive criticisms during every part of the study.

I also thank **Dr. Dr. N. Jeeva M.D., Additional Professor,** and the Medical Registrar **Dr. V. Baskaran M.D.,** for their guidance and encouragement during the study and for permitting to study cases from their unit.

I thank **Dr. P.B. Gopalakrishnan M.D., D.V.,** and his invaluable guidance and perspectives during the study.

I thank **Dr. A. Manimaran M.D., D.T.C.D.,** Assistant professor, Thoracic Medicine, for his guidance in selection of the topic, extensive materialistic support and avid interest that remained a guiding force in the practical execution of the project.

I thank **Dr. S. Palaniyandi M.D.,** and Dr. **P.G. Sankarnarayanan M.D.,** Assistant Professors, who served as a source of moral support during the study

I thank **Dr. V. Jeyaseelan D.NB (Paed)** and **Dr. B. Sudagaran D.V, D.D,** ART medical officers**, Dr. Barathi Suresh Kannan M.B, B.S.,** Medical officer TB Cell, for their materialistic support and suggestions during the study.

I thank all my **patients** without whom this work would not be possible.

AIMS OF THE STUDY

1. To evaluate the clinical, bacteriological and radiological pattern of tuberculosis infection among HIV seropositive individuals in correlation with the CD 4+ counts.

2. To find out the trend of Tuberculosis infection, in HIV seropositive patients in Thanjavur Medical College, a rural center.

3. To Find out the prevalence of Pulmonary Tuberculosis among HIV Seropositives in Thanjavur Medical College.

BACKGROUND OF THE STUDY

Tuberculosis is a life threatening, transmissible and pandemic disease especially among millions of the HIV infected patients. In developing countries like India, where HIV infection is becoming prevalent and where Tuberculosis infection has long been endemic, its incidence is increasing. The following studies were conducted in HIV and Tuberculosis co-infection in INDIA.

1. The trend of HIV infection in patients with pulmonary tuberculosis in South India by Solomon, Anuradha, Dr. S. Rajashekar.
2. The trend of HIV infection in patients with Tuberculosis in rural south India by Dr. S. Rajashekar, A. Uma, A.S. Kamatchi
3. A study on HIV and TB- a comparitive study by Beena susheel and Pai.
4. Prevalence of TB among HIV seropositives in Kolkata by M.K. Bhattarcharya and K. Sarkar.

HIV infected persons are in five-fold risk of developing Tuberculosis than the general population and every third HIV infected person dies of Tuberculosis worldwide.

However no information is available about the prevalence of Tuberculosis among HIV seropositives in Thanjavur Medical College, a rural center in South India, which caters to the needs of about ten districts of Tamil Nadu.

INTRODUCTION

Human immuno deficiency virus infection is becoming a pandemic affecting millions of people in the sub Saharan, South and South East Asian regions.

Human immuno deficiency virus infection has superseded other diseases and has become the major killer disease in the recent past.

Human immuno deficiency virus enters into the human body and destroys the immune frame work thereby predisposing to other infections In developing countries like India where tuberculosis is already a known endemic this growing trend of Human immuno deficiency virus infection becomes significant.

About one third to one half of the patients with Human immuno deficiency virus infection is co infected with tuberculosis and the mortality is more in this group.

So the need of the hour lies in tackling tuberculosis efficiently in persons with Human immuno deficiency virus infection and reducing the mortality in the above group.

TUBERCULOSIS: an overview

Tuberculosis has been present in humans since antiquity, as the origins of the disease are in the first domestication of cattle (which also gave humanity viral poxes). Skeletal remains show prehistoric humans (4000 BC) had TB and tubercular decay has been found in the spines of Egyptian mummies from 3000-2400 BC. There were references to TB in India around 2000 BC, and indications of lung scarring identical to that of modern-day TB sufferers in preserved bodies (such as mummies) suggests that TB was present in The Americas from about 2000 BC

Phthisis is a Greek term for consumption. Around 460 BC, Hippocrates identified phthisis as the most widespread disease of the times which was almost always fatal.

Due to the variety of its symptoms, TB was not identified as a single disease until the 1820s and was not named 'tuberculosis' until 1839 by J. L. Schönlein.

The bacillus-causing tuberculosis, *Mycobacterium tuberculosis*, was identified and described on March 24, 1882 by Robert Koch. He received the Nobel Prize in physiology or medicine in 1905 for this discovery.

The other names for tuberculosis are:

TB (short for *tub*erculosis and also for Tubercle Bacillus)

Consumption (TB seemed to consume people from within with its symptoms of bloody cough, fever, pallor, and long relentless wasting)

Wasting disease

White plague (TB sufferers appear markedly pale)

Phthisis (Greek for consumption) and **phthisis pulmonalis**

King's evil

Miliary TB (x-ray lesions look like millet seeds)

Koch's Disease named after Robert Koch who discovered the tuberculosis bacilli.

Pathogenesis

While only 10% of TB infection progresses to TB disease, if untreated the death rate is 51%.

TB infection begins when MTB bacilli reach the pulmonary alveoli, infecting alveolar macrophages, where the mycobacteria replicate exponentially. The

primary site of infection in the lungs is called the Ghon focus. Bacteria are picked up by dendritic cells, which can transport the bacilli to local (mediastinal) lymph nodes, and then through the bloodstream to the more distant tissues and organs where TB disease could potentially develop: lung apices, peripheral lymph nodes, kidneys, brain, and bone.

Tuberculosis is classed as one of the granulomatous inflammatory conditions. Macrophages, T lymphocytes, B lymphocytes and fibroblasts are among the cells that aggregate to form a granuloma, with lymphocytes surrounding infected macrophages. The granuloma functions not only to prevent dissemination of the mycobacteria, but also provides a local environment for communication of cells of the immune system. Within the granuloma, **T lymphocytes (CD4+)** secrete a cytokine such as interferon gamma, which activates macrophages to destroy the bacteria with which they are infected, making them better able to fight infection. T lymphocytes (CD8+) can also directly kill infected cells.

Importantly, bacteria are not eliminated with the granuloma, but can become dormant, resulting in a latent infection. Latent infection can be diagnosed only by tuberculin skin test, which yields a delayed hypersensitivity type response to purified protein derivatives of M. tuberculosis in an infected person.

Another feature of the granulomas of human tuberculosis is the development of cell death, also called necrosis, in the center of tubercles. To the naked eye this has the texture of soft white cheese and was termed caseous necrosis.

If TB bacteria gain entry to the blood stream from an area of tissue damage they spread through the body and set up myriad foci of infection, all appearing as tiny white tubercles in the tissues. This is called miliary tuberculosis and has a high case fatality.

Progression

In those people in whom TB bacilli overcome the immune system defenses and begin to multiply, there is progression from TB infection to TB disease. This may occur soon after infection (primary TB disease – 1 to 5%) or many years after infection (post primary TB, secondary TB, reactivation TB disease of dormant bacilli – 5 to 9%).

About five percent of infected persons will develop TB disease in the first two years, and another five percent will develop disease later in life. In other words, about 10% of infected persons with normal immune systems will develop TB disease in their lifetime.

Some medical conditions increase the risk of progression to TB disease. In HIV infected persons with TB infection, the risk increases to 10% each year instead

of 10% over a lifetime. Other such conditions include drug injection (mainly because of the life style of IV Drug users), substance abuse, recent TB infection (within two years) or history of inadequately treated TB, chest X-ray suggestive of previous TB (fibrotic lesions and nodules), diabetes mellitus, silicosis, prolonged corticosteroid therapy and other immunosuppressive therapy, head and neck cancers, hematologic and reticuloendothelial diseases (leukemia and Hodgkin's disease), end-stage renal disease, intestinal bypass or gastrectomy, chronic malabsorption syndromes, or low body weight (10% or more below the ideal).

TB disease most commonly affects the lungs (75% or more), where it is called pulmonary TB. Symptoms include a productive, prolonged cough of more than three weeks duration, chest pain, and hemoptysis. Systemic symptoms include fever, chills, night sweats, appetite loss, weight loss, and easy fatigability.

Diagnosis

A complete medical evaluation for TB includes a medical history, a physical examination, a tuberculin skin test, a serological test, a chest X-ray, and microbiologic smears and cultures. Bacteriophage-based assays are among a few new testing procedures that offer the hope of cheap, fast and accurate TB testing for the impoverished countries that need it most.

HIV – an introduction.[1]

In 1981, the first cluster of cases that we now call AIDS was recognized and reported. Nearly all of the early identified cases were in young homosexual men, but it was quickly learned that HIV infection could be transmitted by heterosexual contact and by blood transfer from infected to non infected individuals.

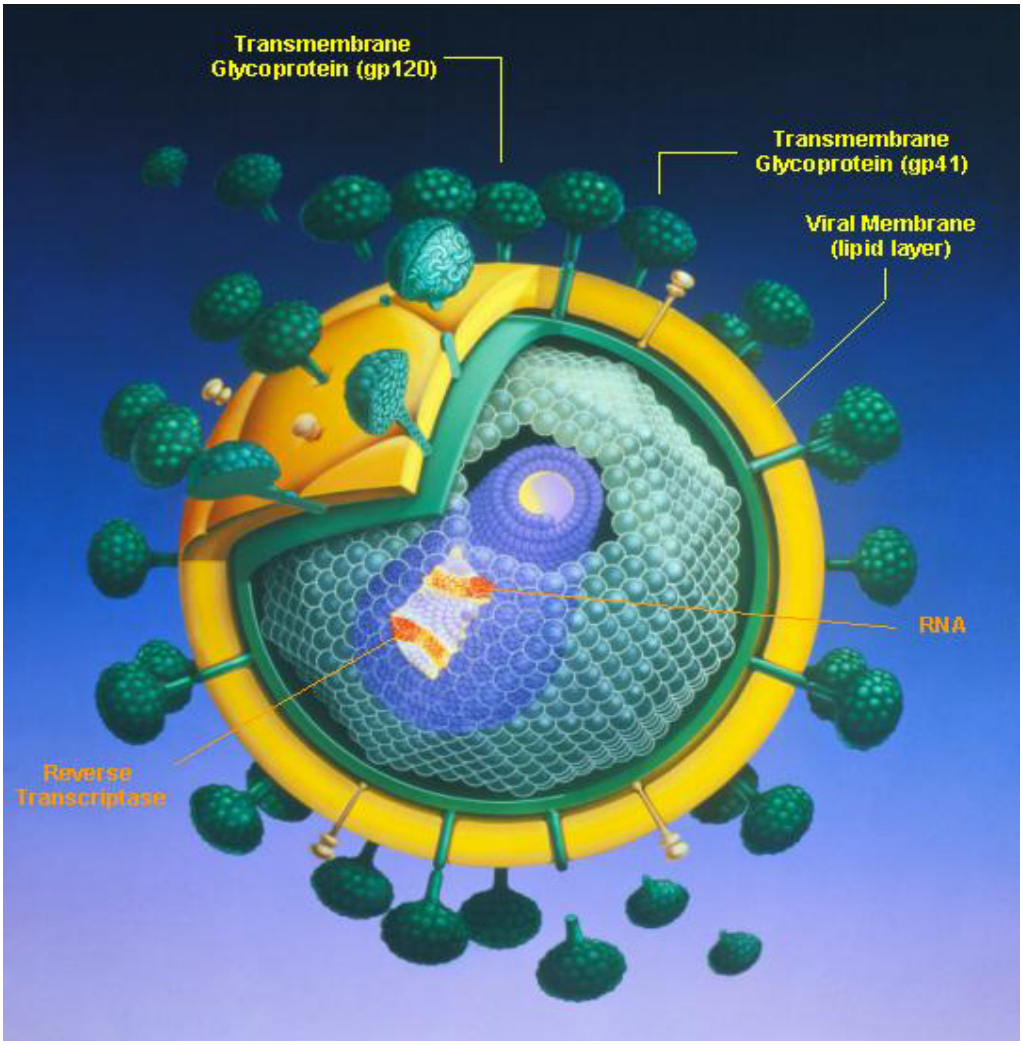
The clinical consequences of human immunodeficiency virus (HIV) infection are due to the ability of this virus to disarm the host immune system, a process that occurs by virtue of the fact that the primary target for the virus is the helper-inducer subset of lymphocytes. This lymphocyte subset, defined by its surface expression of the CD4 molecule, acts as the pivotal orchestrator of a myriad of immune functions. HIV infection can therefore be considered a disease of the immune system, characterized by the progressive loss of CD4-positive (CD4+) lymphocytes, with ultimately fatal consequences for the infected host.

Despite this immunosuppression induced by HIV, a number of specific immunologic defenses against the virus are generated in infected individuals and may contribute to the long asymptomatic phase following infection by keeping the virus at least partially contained.

The hallmark of HIV infection is progressive depletion of the CD4 helper-inducer subset of lymphocytes. Because of the central role of these cells in immunologic functioning, the clinical disease manifestations of immunosuppression and susceptibility to opportunistic infections and neoplasms are not surprising. The immunologic deficits associated with HIV infection are widespread and involve numerous interdependent effector arms of the immune system, including both cellular and humoral elements.

Of all the opportunistic infections in persons infected with HIV virus tuberculosis remains the commonest.

HIV probably increases susceptibility to infection with *M. tuberculosis.* HIV increases the risk of progression of *M. tuberculosis* infection to TB disease. This risk increases with increasing immunosuppression. HIV increases not only the risk but also the rate of progression of recent or latent *M. tuberculosis* infection to disease.



Shown above is the diagram of the **Human immunodeficiency virus** showing the envelope glycoprotein and reverse transcriptase enzyme.

WHO clinical staging system for HIV infection and related disease in adults (13 years or older)[2]

Stage 1: º Asymptomatic

º Persistent generalized lymphadenopathy

Performance scale 1: asymptomatic, normal activity

Stage 2: º Weight loss < 10% of body weight

º Minor mucocutaneous manifestations

(e.g. oral ulcerations, fungal nail infections)

º Herpes zoster within the last 5 years

º Recurrent upper respiratory tract infections

(e.g. bacterial sinusitis)

and/or Performance scale 2: symptomatic, normal activity

Stage 3: º Weight loss > 10% of body weight

º Unexplained chronic diarrhoea for more than 1 month

º Unexplained prolonged fever for more than 1 month

º Oral candidiasis (thrush)

º Oral hairy leukoplakia

º Pulmonary TB

º Severe bacterial infections (pneumonia, pyomyositis)

and/or Performance scale 3: bedridden < 50% of the day during the last month

Stage 4: º HIV wasting syndrome.

º *Pneumocystis carinii* pneumonia

º Toxoplasmosis of the brain

º Cryptosporidiosis with diarrhoea, for more than 1 month

º Cryptococcosis, extrapulmonary

º Cytomegalovirus (CMV) disease of an organ other than liver, spleen, lymph nodes

º Herpesvirus infection, mucocutaneous for more than 1 month, or visceral any duration

º Progressive multifocal leukoencephalopathy (PML)

º Any disseminated endemic fungal infection (e.g. histoplasmosis)

WHO case definitions for AIDS surveillance in adults and children where HIV testing facilities are not available

Adults

The case definition for AIDS is fulfilled if at least 2 major signs and at least 1 minor sign are present.

Major signs

º Weight loss > 10% of body weight

º Chronic diarrhoea for more than 1 month

º prolonged fever for more than 1 month

Minor signs

º Persistent cough for more than 1 month

º generalized pruritic dermatitis

º History of herpes zoster

º oropharyngeal candidiasis

º Chronic progressive or disseminated herpes simplex infection

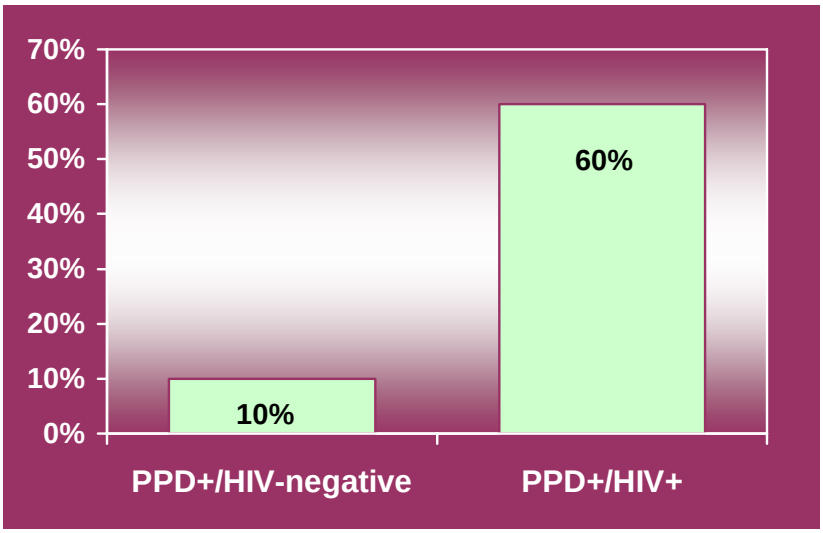
º generalized lymphadenopathy

The presence of either generalized Kaposi sarcoma or cryptococcal meningitis is sufficient for the case definition of AIDS.

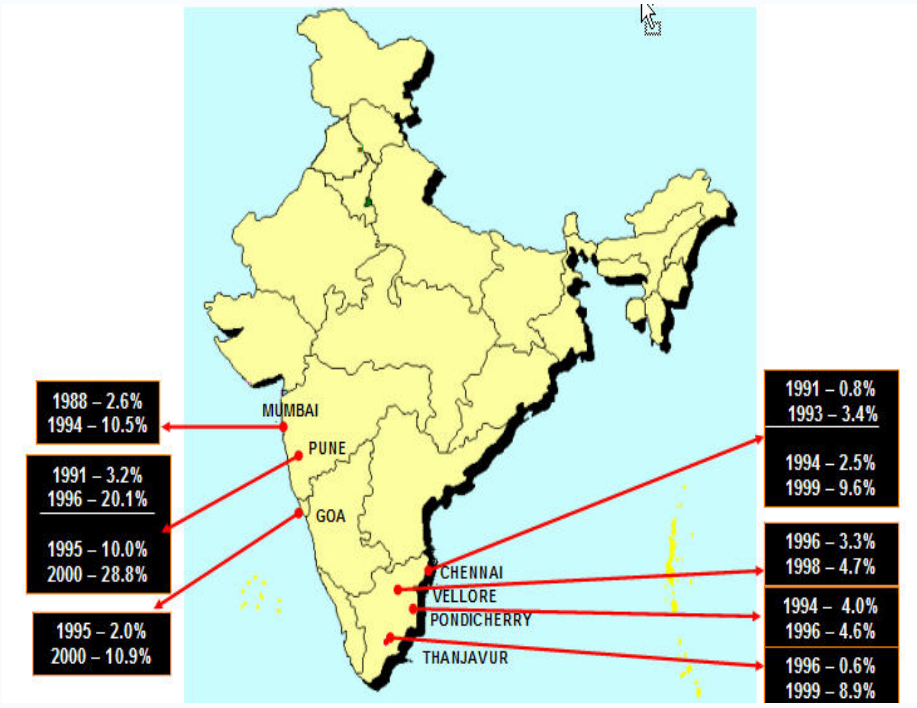
The advantages of this case definition are that it is simple to use and inexpensive. The disadvantages are its relatively low sensitivity and specificity. For example, HIV-negative TB cases could be counted as AIDS cases because of their similarity in clinical presentation.

PRACTICAL POINT

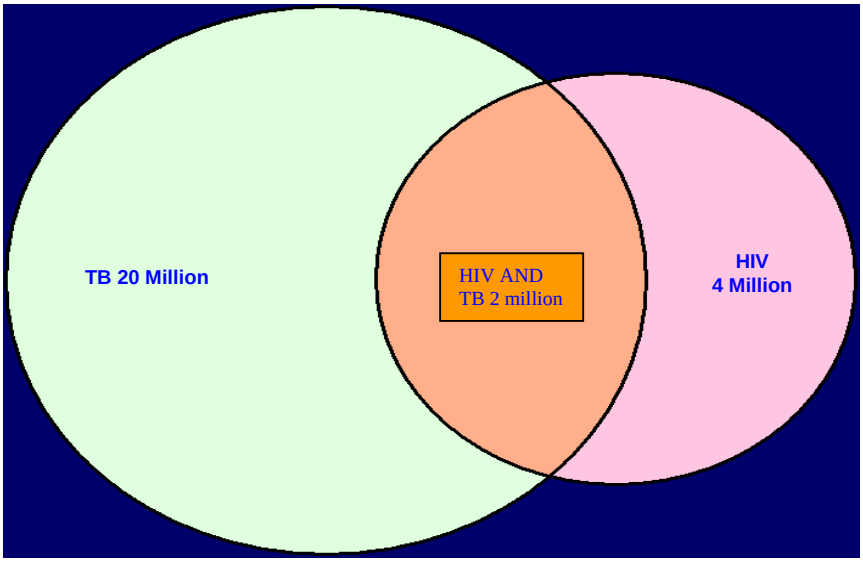
The term AIDS is used for epidemiological surveillance, not for clinical care. a *for patients with TB, persistent cough for more than 1 month should not be considered as a minor sign.*



RISK OF HIV IN TB PATIENTS



HIV AND TB COINFECTION IN SOUTH INDIA.



Picture showing estimated HIV and TB co infection in India

Features	Stage of HIV infection	
	Early	Late
Clinical Presentation	Often resembles Post-primary TB (Adult-type)	Often resembles Primary TB Extra pulmonary TB common
Sputum Smear Result	Often positive	Often negative
Chest X-ray Appearance	Often shows cavities	?Atypical presentation, often infiltrates ?Lower lung-field lesions, intra-thoracic lymph nodes & infrequent cavities

FEATURES AND CLINICAL PRESENTATION IN RELATION TO STAGE OF HIV INFECTION

Tuberculosis in HIV infection:

HIV has had a substantial effect on the incidence, clinical manifestations, treatment, and outcome of TB. Globally, HIV and TB are the 2 leading infectious causes of death.

People who are infected with HIV are at an increased risk of contracting tuberculosis. The WHO estimates that just over 20 million people are currently infected with HIV and of these 6 million are co-infected with *Mycobacterium tuberculosis* so Tuberculosis remains an important problem in patients with human immunodeficiency virus (HIV) infection.

Co infection with these pathogens can be particularly devastating, especially in the developing world, where the burden of disease is high and access to effective therapy is low.

Among infections associated with HIV, tuberculosis (TB) is unique in that it may be transmitted to immunocompetent persons via the respiratory route, is easily treatable once identified, may occur in early-stage HIV disease, and is preventable with drug therapy.

However, multi drug resistance is a potentially serious problem, even though its incidence has declined because of the use of directly observed therapy and other improved practices.

TB is a major opportunistic infection in HIV-infected patients, often representing their AIDS-defining illness and the first indication of immunodeficiency. Epidemiology, clinical manifestations, and management of TB are altered in HIV-infected patients.

Impact of HIV on TB

HIV is the most significant risk factor for progression from sub clinical infection with *Mycobacterium tuberculosis* to active TB [3,4].

However, when a person is dually infected with HIV and *M. tuberculosis*, the risk of developing TB significantly increases from 10% in a life time to 5%–15% per year[5-8]. HIV-infected persons are at markedly increased risk for primary or reactivation tuberculosis[9, 10] and for second episodes of tuberculosis from exogenous reinfection.[11] The lifetime risk for progressing to active TB among HIV-negative persons latently infected with *M. tuberculosis* is estimated at 10%. In contrast, among HIV-infected persons, the risk for progressing to active disease is approximately 10% *per year*,[12] and the immediate risk for progressive primary disease after recent infection with *M. tuberculosis* approaches 40%.[13] This interaction between TB and HIV accounts for much of the recent global resurgence in TB. Of note, however, HIV infection does not increase the infectiousness of persons with active TB.[14] The introduction of potent combination antiretroviral therapy in the developed world, which has

dramatically decreased the risk for opportunistic infections and death among HIV-infected persons, has also decreased the risk for developing active TB[15] and the risk for death among HIV-infected persons who develop active TB[16].

Epidemiology

The frequency with which HIV and Mycobacterium tuberculosis infection occur together is determined by the epidemiology of each disease in a given population. Highest rates are found in the homeless, injecting drug users, and recent immigrants and refugees[17].

The incidence of TB in HIV-infected persons is more than 100 times that of the general population. In untreated HIV-infected persons who have a positive tuberculin skin test, the risk of active TB is about 8% per year [18].

Nosocomial transmission of TB from HIV-infected patients to healthcare workers has been reported [19].

One of the most threatening features of TB in HIV-infected patients has been the spread of multi drug-resistant (MDR) organisms [20]. MDR TB is defined as disease that is resistant to at least two drugs (INH and Rifampicin). Its incidence has declined dramatically in recent years with more rapid case

identification, improved isolation practices, use of early empirical therapy with drugs directed against MDR strains [21], and use of directly observed therapy [22]

Pathogenesis

Tuberculosis can develop through progression of recently acquired infection (primary disease), reactivation of latent infection, or exogenous reinfection.

Infection with M tuberculosis can occur when an individual exposed to an infectious case of tuberculosis inhales particles (<5 µm in size) containing the tubercle bacilli.[23] If the bacilli reach the pulmonary alveoli, they may be ingested by alveolar macrophages, the first line of defense against M tuberculosis. Surviving tubercle bacilli multiply within the macrophage and eventually undergo hematogenous spread to other areas of the body.

Once infection does occur, however, the risk of rapid progression is much greater among persons with HIV infection, because HIV impairs the host's ability to contain new tuberculous infection.

Immunocompetent individuals infected with M tuberculosis have approximately a 10% lifetime risk of developing tuberculosis, [24] with half of the risk occurring in the first 1-2 years after infection.

CD4 cell-mediated immunity and macrophage function are essential in the control of M tuberculosis infection. During primary infection of an immunocompetent host, cell-mediated immunity usually develops and arrests

progression of disease. About 5% of patients whose primary infection is controlled have reactivation years to decades later. In another 5% of patients, infection is not contained, and primary pulmonary, extra pulmonary or disseminated TB can occur.

Susceptibility to tuberculosis is related to the pattern of cytokines produced by T lymphocytes. CD4+ lymphocytes, which produce interferon-γ, are central to antimycobacterial immune defenses, and fatal mycobacterial disease develops in children who lack the interferon-γ receptor.[25] In contrast to CD4+ lymphocytes, CD8+ lymphocytes, which produce interleukin-4 and interleukin-10, do not contribute to antimycobacterial immunity.[26] When peripheral-blood lymphocytes from HIV-infected patients with tuberculosis are exposed to *Mycobacterium tuberculosis* in vitro, they produce less interferon-γ but similar amounts of interleukin-4 and interleukin-10, as compared with lymphocytes from HIV-negative patients with tuberculosis.[27] These findings suggest that the reduced CD4+ response in HIV-infected patients contributes to their susceptibility to tuberculosis.

The hallmark of HIV infection is progressive deterioration and depletion of CD4 cells, coupled with defects in macrophage and monocyte function [28]. There is evidence that the immune response in patients with TB might enhance HIV viral replication and accelerate the natural progression of HIV infection [29].

The risk of TB developing in an HIV-infected patient who is latently co-infected with M tuberculosis approaches 10% per year, as opposed to a 10% lifetime risk in an immunocompetent host [30]. Patients with more advanced HIV infection (CD4 count, <200 cells/mm3) who are newly infected with M.tuberculosis may lack the ability to contain the primary infection, which can progress rapidly and is fatal if not treated. Infection with M tuberculosis in an immunocompetent person is thought to confer significant protective immunity against exogenous reinfection.[24] However, reinfection has been reported in HIV-seronegative[31,32] and -seropositive individuals,[33-37] although its incidence is not known

Tuberculosis and the Course of HIV Infection

Exposure of alveolar macrophages and lymphocytes from HIV-infected patients to *M. tuberculosis* in vitro up-regulates retroviral replication.[38,39]

TB has been associated with a 5- to 160-fold increase in HIV viral replication, which may decrease after successful TB treatment.[40]

Pleural fluid from patients with tuberculosis increases HIV replication in activated lymphocytes,[41] and in HIV-infected patients with pulmonary tuberculosis, the concentrations of retroviral RNA in bronchoalveolar-lavage fluid are highest in areas of tuberculous involvement.[42] *M. tuberculosis*

probably increases HIV replication by inducing macrophages to produce tumor necrosis factor-α, interleukin-1, and interleukin-6.[41,42]

Clinical studies have shown the detrimental effects of tuberculosis on the course of HIV infection. The risk of death in HIV-infected patients with tuberculosis was reported to be twice that in HIV-infected patients without tuberculosis, independently of the CD4 cell count.[43] The high mortality rate among patients with tuberculosis appeared to be due to progressive HIV infection rather than tuberculosis. The degree of immunosuppression is the most important predictor of survival in HIV-infected patients with tuberculosis, since negative tuberculin skin tests, prior opportunistic infections, and low CD4 cell counts are associated with increased mortality.[44,45]

Clinical presentation

Unlike other opportunistic infections, TB can occur in persons with early-stage HIV infection (CD4 count, >300 cells/mm3). Clinical presentation of TB in such patients is similar to that in healthy hosts with reactivation disease [46]. Patients are less likely to present with extrapulmonary disease at this stage of HIV infection. Because of the increased virulence in immunocompetent hosts of M tuberculosis compared with other opportunistic pathogens (e.g., Pneumocystis jiroveci), tuberculosis can occur early in the course of HIV infection. In several studies of HIV-infected patients with pulmonary

tuberculosis, the median CD4 T-cell count was >300 cells/mm3. (38) However, in patients with primarily extrapulmonary involvement or disseminated disease, the CD4 T-cell count may be much lower. For example, two studies in African patients with disseminated disease found the median CD4 T-cell count to be <80 cells/mm3.[47] A prospective study in the United States,[48] found the median CD4 T-cell count to be 144 cells/mm3 (range 2-543) in HIV-infected patients with all forms

of tuberculosis. Although tuberculosis can be a relatively early manifestation of HIV-1 infection, it is important to note that the risk of developing tuberculosis, and of disseminated infection, increases as the CD4 T-cell count decreases.

Typical symptoms include fever, weight loss, productive cough of several weeks' duration, and hemoptysis. Chest radiographs demonstrate the presence of focal infiltrates and/or cavitation involving the upper lobes.

In patients with advanced HIV disease, TB may present atypically and extrapulmonary TB is more common. Disseminated disease with involvement of bone marrow, bone, urinary and gastrointestinal tracts, liver, regional lymph nodes, and the central nervous system is common [30, 46].

Radiographic Findings

The chest radiograph is the cornerstone of diagnosis for pulmonary tuberculosis. Upper lobe infiltrates and cavities are the typical findings in reactivation tuberculosis, whereas intrathoracic lymphadenopathy and lower

lobe disease are seen in primary tuberculosis. In HIV-infected persons with higher CD4 T-cell counts (e.g., >200 cells/mm3) the radiographic pattern tends to be one of reactivation disease with upper lobe infiltrates with or without cavities. [49] In HIV-infected persons who have a greater degree of immunosuppression (e.g., CD4 T-cell count <200 cells/mm3), a pattern of primary disease with intrathoracic lymphadenopathy and lower lobe infiltrates is seen (Figure 2 and Figure 3). As chest radiographs may appear normal in 7-14% of cases, a high index of suspicion must be maintained in evaluating an HIV-infected patient with symptoms suggestive of tuberculosis. [50,51] .The finding of low-density lymph nodes with peripheral enhancement on a contrast-enhanced chest computed tomography (CT) scan is highly predictive of tuberculosis.

Chest radiographs may be normal or show evidence of perihilar or mediastinal lymphadenopathy without parenchymal lung involvement. Radiographs and clinical presentation may mimic community-acquired pneumonia or Pneumocystis carinii pneumonia. Cavitation is unusual at this stage of advanced immunosuppression, and infiltrates more often are diffuse or interstitial. Mycobacterial blood cultures may yield M tuberculosis in one third of patients with advanced HIV immunosuppression [52] a severely immunocompromised person presenting with TB may not show cavitation and may have only mild interstitial infiltrates. Pneumonia, lung tumors, and fungal

masses may also occur at the site of previously healed TB or granulomatous lesions.

Testing for HIV Infection in Patients with Tuberculosis

All patients with tuberculosis should be tested for HIV co infection because of the potential benefits of an early diagnosis of HIV infection.[53]

Selective HIV testing in patients with tuberculosis is unwise, because health care providers often fail to identify risk factors for HIV related to heterosexual transmission.[54] Even when patients with tuberculosis are questioned about risk factors for HIV infection, up to 5 percent of those who report no risk factors are infected with HIV.[54]

Diagnosis

In patients with TB and HIV infection, special consideration is required in assessing results of tuberculin skin test and acid-fast bacillus smear and culture.

Tuberculin skin test

HIV infection causes depression of cell-mediated immunity, which can reduce the sensitivity and reliability of the tuberculin skin test. Only 30% to 50% of HIV-infected patients who are co infected with M tuberculosis have a

positive result on the tuberculin skin test [46]. Although a positive result increases the likelihood of TB, a negative result does not exclude the diagnosis.

Therefore, diagnostic evaluation for TB should be undertaken in all patients who have clinical features compatible with TB, regardless of the results of the tuberculin skin test. Several cohort studies have demonstrated a high incidence of active tuberculosis among HIV-infected individuals with positive tuberculin skin test results.

There are recent reports of restoration of delayed hypersensitivity on skin testing, including tuberculin skin testing in HIV-infected patients who begin highly active antiretroviral therapy. This reaction reflects restoration of the anti-M tuberculosis cell-mediated immune response, a phenomenon that usually occurs within the first month of therapy [55].

Acid-fast bacillus smear and culture

In HIV-infected patients with pulmonary TB, cultures are positive in about 90% of cases and sputum smears are positive in about 50% to 70%--numbers that are similar to those seen in immunocompetent adults with reactivation TB [56].

Polymerase chain reactions and gene probes are approved for rapid identification of M tuberculosis in sputum smears that are positive for acid-fast bacilli. These rapid tests are more sensitive than traditional staining methods but are not as sensitive as culture. Smears from extrapulmonary sites (e.g., bone marrow, lymph nodes) are often negative for acid-fast bacilli. However, the sensitivity of culture approaches 90%, depending on the number of samples tested [57].

Bacteriologic Examinations

All patients suspected of having pulmonary tuberculosis should have 3 sputum specimens obtained on 3 consecutive days, and these specimens should be examined for AFB and cultured for mycobacteria. AFB identified on smear is not diagnostic of tuberculosis, as the acid-fast stain detects mycobacteria other than M tuberculosis, including M avium-intracellulare complex or M kansasii. However, until identification is confirmed, empiric therapy for tuberculosis should be initiated if the sputum smear is positive for AFB. The rate of AFB smear positivity has varied from 31% to 89% in HIV-positive patients. [58] In general, the rate of smear positivity correlates with the extent of radiographic disease. For example, patients with cavitary lesions due to active tuberculosis will almost always have positive smears, whereas a negative smear in a patient with minimal disease on chest radiograph would not be unusual, and

would not rule out active tuberculosis. However, in HIV-infected patients positive smears may be seen with relatively little radiographic involvement.

When expectorated sputum specimens are AFB smear-negative, further evaluation may be indicated. Bronchoscopy with bronchoalveolar lavage and transbronchial biopsy may be useful in the evaluation of an abnormal chest radiograph when sputum smears are negative. In this setting, a rapid diagnosis of presumptive tuberculosis, based on histology and AFB smear of specimens obtained by bronchoscopy, can be made in 30-40% of individuals, which is similar to the yield of bronchoscopy in HIV-negative cases with smear-negative pulmonary tuberculosis. [59].

Positive cultures for M tuberculosis provide a definitive diagnosis of tuberculosis. Approximately 15% of reported tuberculosis cases are culture negative, but these data are not available for HIV-infected cases. However, at San Francisco General Hospital, culture-negative tuberculosis in HIV-infected patients is seldom observed. (This perceived increase in sensitivity might be due in part to the increased use of diagnostic bronchoscopy in HIV-positive cases of suspected tuberculosis.) Unfortunately, culture results may not be available for 2-6 weeks, creating a need for more rapid diagnostic techniques.

Nucleic acid amplification (NAA) tests detect nucleic acid sequences unique to organisms in the M tuberculosis complex, allowing for a rapid

diagnosis. Two NAA tests, the Amplified Mycobacterium Tuberculosis Direct Test (MTD; Gen-Probe) and the Amplicor Mycobacterium Tuberculosis Test (Amplicor; Roche) have been approved by the U.S. Food and Drug Administration (FDA) for use in respiratory specimens in patients who have not previously been treated for tuberculosis. The MTD test is approved for use in smear-positive or smear-negative samples, whereas Amplicor is only approved for use with smear-positive samples.

A negative NAA test does not rule out the diagnosis of active tuberculosis, and antituberculous therapy and further diagnostic workup are needed if sufficient clinical suspicion for tuberculosis exists. The predictive value of NAA testing will vary depending on the sensitivity and specificity of the test in the local laboratory, as well as on the prevalence of M tuberculosis and other mycobacteria. Moreover, NAA testing does not provide information on drug resistance. NAA tests are an important addition to our armamentarium of diagnostic tools, but they do not replace AFB smear, culture, or, more importantly, clinical judgment.

Diagnosis of Latent Tuberculosis Infection

Screening for latent tuberculosis infection (LTBI) is an essential step in controlling the spread of tuberculosis. Screening for LTBI is recommended in persons at risk for recent infection and in those groups with increased risk of progression to active disease once infected, including HIV-infected persons.

The tuberculin skin test (Mantoux method) is currently the only method available for identifying LTBI. Routine annual tuberculin skin testing is recommended in HIV-infected individuals.

A reaction of >=5 mm induration is considered positive for HIV-infected patients and persons with other forms of severe immunosuppression, persons who are close contacts of infectious cases, and persons with abnormal chest radiographs consistent with tuberculosis.[60]. Use of the 5-mm cutoff is supported by a prospective study in the United States demonstrating that the risk of tuberculosis was significantly higher in HIV-infected persons with tuberculin skin test reactions >=5 mm of induration than in those who have a reaction <5 mm.[48]

It is important to keep in mind that a negative tuberculin skin test does not exclude infection or active disease. Testing with tuberculin purified protein derivative is dependent on the presence of an intact cell-mediated immune response. In the setting of HIV infection, reduced cell-mediated immunity can lead to decreased delayed-type hypersensitivity (DTH) responsiveness, resulting in False-negative skin tests. In a multicenter study in the United States, the prevalence of a positive tuberculin skin test (>=5 mm) was shown to decrease with decreasing CD4 T-cell counts.[61]

Persons who are at risk for tuberculous infection (e.g., injection drug users, individuals who are institutionalized or from high-prevalence regions)

should have a chest radiograph performed even if the tuberculin skin test is negative, particularly if their CD4 T-cell count is low. Annual chest radiographs should be considered in this high-risk group.

Application of multiple skin test antigens (e.g., Candida, mumps, tetanus toxoid, etc.), referred to as anergy testing, has been used to assess cell-mediated immune function and to distinguish true-negative from false-negative tuberculin skin test results. In 1991, the CDC recommended that anergy testing be performed in conjunction with tuberculin skin testing in HIV-infected persons based on the premise that anergic HIV-infected individuals at high risk for tuberculosis infection would benefit from treatment with INH. [62] In 1997, the CDC revised its recommendations and no longer recommends anergy testing while screening for M tuberculosis infection in HIV-infected persons. [63] The revised recommendation is based on the following points. First, there are no standardized guidelines for performing anergy skin testing. The appropriate number of control antigens to administer or the appropriate cut-off for interpreting a test as positive is not known. Second, the response to skin testing with control antigens as well as with tuberculin can vary over time. Several studies have demonstrated that HIV-1-seropositive individuals can regain DTH responsiveness with time. [64, 65, 66] In a multicenter study, Chin and colleagues[66] reported that 31% of anergic HIV-1-seropositive patients responded to DTH testing 1 year later. The only factor associated with regaining DTH

responsiveness was the CD4 T-cell count: the higher the CD4 count, the more likely the individual was to regain DTH responsiveness. Finally, treatment of LTBI in anergic HIV-infected persons has not been demonstrated to be beneficial.[67, 68]

In some individuals with tuberculous infection, DTH responsiveness may decrease with time. A second tuberculin skin test, applied weeks to months after the first, can "boost" the DTH response resulting in a positive skin test reaction. Such responses are considered true evidence of tuberculous infection. In a multicenter study in the United States, only 2.7% of HIV-1-seropositive patients "boosted" the tuberculin reaction with a second tuberculin skin test, despite relatively high demographic risk of tuberculous infection.[69] However, a study in Uganda found that 17 (29%) of 58 HIV-1-infected subjects responded to a second tuberculin skin test.[70]

Natural history

Although the immune response to M tuberculosis is important in controlling disease, immune activation may also be associated with increased HIV viral load and accelerated progression of HIV infection. A retrospective cohort study in the United States found that although only one patient in the group died of tuberculosis, HIV-infected patients with tuberculosis do not survive as long as HIV-infected controls without tuberculosis, even after controlling for baseline CD4 T-cell count. When tuberculin-positive HIV-

infected patients were given INH therapy in Haiti, they were less likely to develop AIDS and less likely to die than patients given placebo. [71] Thus, it is likely that tuberculosis acts to accelerate the clinical course of HIV infection.

Although increased viral replication is thought to play a role, the mechanisms by which tuberculosis accelerates progression of HIV disease are not known with certainty. High levels of tumor necrosis factor (TNF)-alpha, which are known to increase HIV replication in T-cell clones,[72] have been demonstrated in both HIV-1-seropositive and -seronegative tuberculosis cases.[73].

Moreover, Investigators have shown that M tuberculosis or purified protein derivative can also increase viral replication in infected T lymphocytes and monocytes.[74-76]A recent study demonstrated a 5- to 160-fold increase in viral replication during the acute phase of untreated tuberculosis.[72] The clinical significance of this increase in viral load is uncertain.

TREATMENT

STANDARD TREATMENT REGIMENS

Anti-TB therapy is equally effective in HIV-negative and HIV-positive patients. The weight of the evidence to date indicates that the rate of TB relapse after short-course (6-month rifamycin-based) therapy is similar for HIV-positive and HIV-negative patients, although this remains somewhat controversial.[77,78].

In general, then, the same treatment regimen may be used regardless of HIV status. The American Thoracic Society TB treatment guidelines (currently under revision) will likely include a recommendation to extend the duration of therapy to 9 months (regardless of HIV status) in persons who have both cavitary pulmonary disease on initial presentation and positive-sputum cultures after 2 months of treatment. These changes are based on results of a recent TB-treatment study conducted by the CDC, in which HIV-negative adults with pulmonary disease who met these criteria had a relapse rate of >20% -- far higher than the clinically acceptable relapse rate of <5%.[79]

In TB-endemic areas, recurrent TB after completion of a course of therapy is more likely to be due to exogenous reinfection than to relapse.[80.] Compared with HIV-negative TB patients, co infected patients have a higher risk for recurrent TB, but this is due to reinfection rather than relapse.[81] In a study conducted in Haiti, HIV-infected persons who completed a course of TB therapy were less likely to develop recurrent TB if they received a 12-month post-treatment course of isoniazid, compared with persons who received placebo.[82] However, such practice has been implemented neither in developing countries (due to insufficient infrastructure) nor in developed countries (due to lower TB incidence rates and lower rates of exogenous reinfection).

PHARMACOKINETIC INTERACTIONS

A central aspect of TB treatment in HIV-infected patients is the pharmacokinetic interactions between rifamycins (e.g., rifampin and rifabutin) and PIs and NNRTIs. Although these interactions do not preclude the concomitant use of potent antiretroviral therapy and anti-TB therapy, clinicians must be aware of these interactions and adjust dosages accordingly. Although large studies of the effectiveness of rifabutin-based regimens in co infected patients concomitantly receiving antiretroviral therapy are underway, the results will not be available for 1 to 2 years. However, 2 small studies have demonstrated that rifabutin-based regimens are well tolerated and effective in such patients.[83], [84]

DIRECTLY OBSERVED THERAPY

Self-administered TB therapy has been compared with directly observed therapy in very few well designed, randomized, controlled studies; however, the available data indicate that directly observed therapy is associated with decreased rates of TB incidence and drug resistance[85] and increased rates of sputum conversion and therapy completion.[86] Among HIV-infected patients, directly observed therapy has been associated with improved survival.[87] Because of these benefits, directly observed TB therapy is recommended by the American Thoracic Society, the CDC, and the WHO.[88], [89]

The regimen of DOTS is as shown below:

Category of Treatment	Type of patient	Regimen	Sputum Examination
CAT-I	New sputum smear positive Seriously ill sputum-negative Seriously -ill-EP	2 H3R3Z3E3/ 4 H3R3	0 2 4 6 3 5 7 MONTHS
CAT- II	Sputum smear + Relapse, Failure ,Treatment after Default	3 H3R3Z3E3S3/ 1 H3R3Z3E3/ 5 H3R3E3.	0 3 5 8 4 6 9
CAT-III	Sputum negative not seriously ill ,EP not seriously ill	2 H3R3Z3/ 4 H3R3	0 2 6

Abbreviations:

H- INH, R- Rifampicin, Z- Pyrazinamide, E- Ethambutol, S-Streptomycin.

HIV AND PARADOXICAL WORSENING OF TB

Paradoxical worsening of TB is the development of new signs or symptoms of TB disease or the exacerbation of existing manifestations of TB in patients receiving appropriate anti-TB therapy. Diagnosis of paradoxical worsening requires that other possible explanations be excluded, such as treatment failure, drug resistance, poor compliance, malabsorption, adverse drug reactions, and lymphoma. Paradoxical worsening is thought to represent an improvement of the host's immune response to mycobacterial antigens during the course of treatment, leading to more intense inflammation at sites of TB disease.

The estimated incidence of paradoxical worsening of TB in HIV-infected patients ranges from 7% to 36%, which is higher than the rate seen in HIV-negative patients. In one hospital-based study, higher rates of paradoxical worsening in co infected patients were associated with the use of antiretroviral therapy.[90] In a retrospective study of HIV-infected patients receiving outpatient TB treatment, the incidence of paradoxical worsening was not associated with the use of potent combination antiretroviral therapy, but patients experiencing paradoxical worsening while on antiretroviral therapy had a more severe and prolonged course. Paradoxical worsening of TB in HIV-infected patients has been associated with the presence of concurrent pulmonary and extrapulmonary TB at the time of initial diagnosis.[91]

The course of paradoxical worsening can be brief or prolonged, with multiple recurrences and exacerbations. Corticosteroid treatment of severe episodes of paradoxical worsening has not been associated with progression of TB disease or failure of anti-TB therapy. Patients with less severe symptoms may obtain relief with nonsteroidal anti-inflammatory medications. Although antiretroviral therapy may be associated with the development or severity of paradoxical worsening, discontinuation of therapy is not generally recommended.

TREATMENT OF LATENT TB INFECTION

As noted above, the risk for progressing to active TB is high among HIV-seropositive persons infected with *M. tuberculosis*. Therefore, all HIV-infected persons with evidence of latent *M. tuberculosis* infection should receive treatment. See Table 1 for the indications for treatment of latent infection in HIV-infected persons and potential treatment regimens. In a study among HIV-infected persons with latent *M. tuberculosis* infection, 2 months of daily rifampin + pyrazinamide was as effective as 12 months of daily isoniazid in preventing active TB; both regimens were well tolerated.[92] A recent study found that combination short-course regimens had a more durable protective effect than did isoniazid alone.[93.] However, there have recently been 6 hepatotoxicity-associated deaths reported among persons taking daily rifampin + pyrazinamide.[94], [95] Although none of the 6 persons was HIV-positive, the

recommendations for the treatment of latent TB infection have been revised to state that this regimen should not be offered to patients with underlying liver disease or with prior isoniazid-associated hepatotoxicity. This regimen should be used with particular caution in patients concurrently taking other medications associated with liver injury and in those with a history of alcohol abuse. See Table 1 for recommendations for toxicity monitoring during treatment for latent TB infection.

The WHO recommends treating latent *M. tuberculosis* infection in HIV-infected persons in the developing world. However, implementation of this policy has been incomplete due to limited resources in these settings. This is particularly true in settings in which resources are insufficient to identify and treat all persons with active TB, which remains a higher priority.

WHO recommendations for the treatment of TB and HIV co infection with reference to CD-4 cell count.

CD 4 cell count	**Recommended regimen**	**Comments**
< 200 mm^3	Start TB treatment. Start ART as soon as TB treatment is tolerated (2 weeks to 2 months) EFV containing regimens.	Recommended ART EFV is contraindicated in pregnant or women of childbearing potential without effective contraception
200 to 350 mm^3	Start TB treatment. start one of the below regimens after initiation phase: EFV containing regimens or NVP containing regimens in case of Rifampicin free continuation phase TB treatment regimen.	Consider ART
> 350 mm^3	Start TB treatment.	Defer ART
CD 4 count not available	Start TB treatment.	Consider ART

Abbreviations:

EFV- efavirenz, NVP – nevirapine.

MATERIALS AND METHODS

Methodology

Persons who reported having high-risk factors for the HIV infection were screened for HIV status at the Voluntary Counseling and Testing Center at both Thanjavur Medical College and The Raja Mirasudar Hospital, attached to the Thanjavur Medical College, from April 2005 to March 2006.

Screening of HIV infection was done by ELISA rapid diagnostic tests,

1. Immunoblot,
2. Combaids and
3. Tridot Methods.

Patients who were positive in at least two of these three tests were considered positive for HIV infection.

A brief History of illness was taken from the seropositive individuals and these patients were subjected to the following further investigations that include,

Blood Hemoglobin,

Total count,

Differential count,

Erythrocyte Sedimentation Rate,

Liver Function Test,

Sputum Microscopic Examination for Acid Fast Bacilli,

Chest X-Ray PA view,

Mantoux test and

CD-4+ cell count.

Blood Hemoglobin, Total count, Differential count, ESR were all done using the conventional Laboratory methods.

Sputum Examination: Two spot and one early morning sputum samples were examined for Acid Fast Bacilli (AFB) positivity using the Ziehl-Nielsen technique.

CD –4 + cell count was done using FACS Analyzer.

Patients were considered to be suffering from Tuberculosis if,

1. Sputum is positive for AFB.
2. The Mantoux test reading shows induration above 5mm.

3. X-Ray features were suggestive of Tuberculosis. Since there is a high reporting of both inter-observer and intra-observer variations, opinions were obtained from three persons separately – a general physician, a thoracic physician and a radiologist and their Tuberculosis status confirmed.

INCLUSION CRITERIA:

Patients, who are found seropositive with stigmata for tuberculosis like fever, cough with expectoration lasting for more than three weeks, loss of appetite and loss of weight.

Patients with Tuberculous Pleural Effusion were included in the study.

EXCLUSION CRITERIA:

1. Patients who are suffering from Extra-pulmonary Tuberculosis infections like TB Pericarditis, TB meningitis, TB Abdomen, isolated TB lymphadenopathy, Potts Spine and other seriously ill patients.
2. Patients found to have positivity in only one of the three ELISA tests.

3. No consensus among all the three independent observers regarding the X-Ray features of Tuberculosis infection.

STUDY LIMITATIONS:

The confirmation of HIV infection could not be done by Western Blot analysis.

The sputum positivity for tuberculosis infection in HIV infected individuals is low when compared with sero-negative individuals. Hence, for confirmation of Tuberculosis infection in these seropoitive individuals, sputum culture must be done which could not be done in our study.

TUBERCULOSIS: an overview

Tuberculosis has been present in humans since antiquity, as the origins of the disease are in the first domestication of cattle (which also gave humanity viral poxes). Skeletal remains show prehistoric humans (4000 BC) had TB and tubercular decay has been found in the spines of Egyptian mummies from 3000-2400 BC. There were references to TB in India around 2000 BC, and indications of lung scarring identical to that of modern-day TB sufferers in preserved bodies (such as mummies) suggests that TB was present in The Americas from about 2000 BC

Phthisis is a Greek term for consumption. Around 460 BC, Hippocrates identified phthisis as the most widespread disease of the times which was almost always fatal.

Due to the variety of its symptoms, TB was not identified as a single disease until the 1820s and was not named 'tuberculosis' until 1839 by J. L. Schönlein.

The bacillus-causing tuberculosis, *Mycobacterium tuberculosis*, was identified and described on March 24, 1882 by Robert Koch. He received the Nobel Prize in physiology or medicine in 1905 for this discovery.

The other names for tuberculosis are:

TB (short for *tub*erculosis and also for Tubercle Bacillus)

Consumption (TB seemed to consume people from within with its symptoms of bloody cough, fever, pallor, and long relentless wasting)

Wasting disease

White plague (TB sufferers appear markedly pale)

Phthisis (Greek for consumption) and **phthisis pulmonalis**

King's evil

Miliary TB (x-ray lesions look like millet seeds)

Koch's Disease named after Robert Koch who discovered the tuberculosis bacilli.

Pathogenesis

While only 10% of TB infection progresses to TB disease, if untreated the death rate is 51%.

TB infection begins when MTB bacilli reach the pulmonary alveoli, infecting alveolar macrophages, where the mycobacteria replicate exponentially. The

primary site of infection in the lungs is called the Ghon focus. Bacteria are picked up by dendritic cells, which can transport the bacilli to local (mediastinal) lymph nodes, and then through the bloodstream to the more distant tissues and organs where TB disease could potentially develop: lung apices, peripheral lymph nodes, kidneys, brain, and bone.

Tuberculosis is classed as one of the granulomatous inflammatory conditions. Macrophages, T lymphocytes, B lymphocytes and fibroblasts are among the cells that aggregate to form a granuloma, with lymphocytes surrounding infected macrophages. The granuloma functions not only to prevent dissemination of the mycobacteria, but also provides a local environment for communication of cells of the immune system. Within the granuloma, **T lymphocytes (CD4+)** secrete a cytokine such as interferon gamma, which activates macrophages to destroy the bacteria with which they are infected, making them better able to fight infection. T lymphocytes (CD8+) can also directly kill infected cells.

Importantly, bacteria are not eliminated with the granuloma, but can become dormant, resulting in a latent infection. Latent infection can be diagnosed only by tuberculin skin test, which yields a delayed hypersensitivity type response to purified protein derivatives of M. tuberculosis in an infected person.

Another feature of the granulomas of human tuberculosis is the development of cell death, also called necrosis, in the center of tubercles. To the naked eye this has the texture of soft white cheese and was termed caseous necrosis.

If TB bacteria gain entry to the blood stream from an area of tissue damage they spread through the body and set up myriad foci of infection, all appearing as tiny white tubercles in the tissues. This is called miliary tuberculosis and has a high case fatality.

Progression

In those people in whom TB bacilli overcome the immune system defenses and begin to multiply, there is progression from TB infection to TB disease. This may occur soon after infection (primary TB disease – 1 to 5%) or many years after infection (post primary TB, secondary TB, reactivation TB disease of dormant bacilli – 5 to 9%).

About five percent of infected persons will develop TB disease in the first two years, and another five percent will develop disease later in life. In other words, about 10% of infected persons with normal immune systems will develop TB disease in their lifetime.

Some medical conditions increase the risk of progression to TB disease. In HIV infected persons with TB infection, the risk increases to 10% each year instead

of 10% over a lifetime. Other such conditions include drug injection (mainly because of the life style of IV Drug users), substance abuse, recent TB infection (within two years) or history of inadequately treated TB, chest X-ray suggestive of previous TB (fibrotic lesions and nodules), diabetes mellitus, silicosis, prolonged corticosteroid therapy and other immunosuppressive therapy, head and neck cancers, hematologic and reticuloendothelial diseases (leukemia and Hodgkin's disease), end-stage renal disease, intestinal bypass or gastrectomy, chronic malabsorption syndromes, or low body weight (10% or more below the ideal).

TB disease most commonly affects the lungs (75% or more), where it is called pulmonary TB. Symptoms include a productive, prolonged cough of more than three weeks duration, chest pain, and hemoptysis. Systemic symptoms include fever, chills, night sweats, appetite loss, weight loss, and easy fatigability.

Diagnosis

A complete medical evaluation for TB includes a medical history, a physical examination, a tuberculin skin test, a serological test, a chest X-ray, and microbiologic smears and cultures. Bacteriophage-based assays are among a few new testing procedures that offer the hope of cheap, fast and accurate TB testing for the impoverished countries that need it most.

HIV – an introduction.[1]

In 1981, the first cluster of cases that we now call AIDS was recognized and reported. Nearly all of the early identified cases were in young homosexual men, but it was quickly learned that HIV infection could be transmitted by heterosexual contact and by blood transfer from infected to non infected individuals.

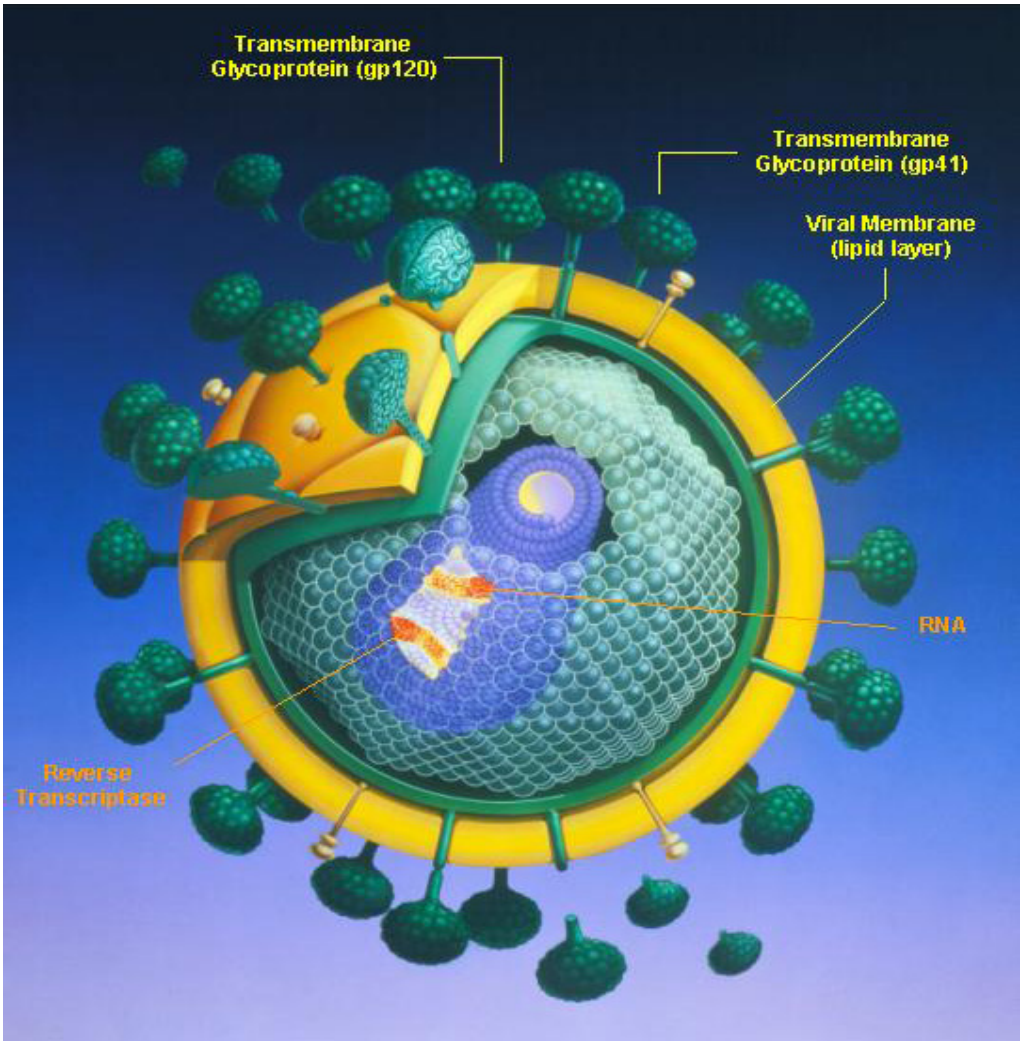
The clinical consequences of human immunodeficiency virus (HIV) infection are due to the ability of this virus to disarm the host immune system, a process that occurs by virtue of the fact that the primary target for the virus is the helper-inducer subset of lymphocytes. This lymphocyte subset, defined by its surface expression of the CD4 molecule, acts as the pivotal orchestrator of a myriad of immune functions. HIV infection can therefore be considered a disease of the immune system, characterized by the progressive loss of CD4-positive (CD4+) lymphocytes, with ultimately fatal consequences for the infected host.

Despite this immunosuppression induced by HIV, a number of specific immunologic defenses against the virus are generated in infected individuals and may contribute to the long asymptomatic phase following infection by keeping the virus at least partially contained.

The hallmark of HIV infection is progressive depletion of the CD4 helper-inducer subset of lymphocytes. Because of the central role of these cells in immunologic functioning, the clinical disease manifestations of immunosuppression and susceptibility to opportunistic infections and neoplasms are not surprising. The immunologic deficits associated with HIV infection are widespread and involve numerous interdependent effector arms of the immune system, including both cellular and humoral elements.

Of all the opportunistic infections in persons infected with HIV virus tuberculosis remains the commonest.

HIV probably increases susceptibility to infection with *M. tuberculosis.* HIV increases the risk of progression of *M. tuberculosis* infection to TB disease. This risk increases with increasing immunosuppression. HIV increases not only the risk but also the rate of progression of recent or latent *M. tuberculosis* infection to disease.



Shown above is the diagram of the **Human immunodeficiency virus** showing the envelope glycoprotein and reverse transcriptase enzyme.

WHO clinical staging system for HIV infection and related disease in adults (13 years or older)[2]

Stage 1: º Asymptomatic

º Persistent generalized lymphadenopathy

Performance scale 1: asymptomatic, normal activity

Stage 2: º Weight loss < 10% of body weight

º Minor mucocutaneous manifestations

(e.g. oral ulcerations, fungal nail infections)

º Herpes zoster within the last 5 years

º Recurrent upper respiratory tract infections

(e.g. bacterial sinusitis)

and/or Performance scale 2: symptomatic, normal activity

Stage 3: º Weight loss > 10% of body weight

º Unexplained chronic diarrhoea for more than 1 month

º Unexplained prolonged fever for more than 1 month

º Oral candidiasis (thrush)

º Oral hairy leukoplakia

º Pulmonary TB

º Severe bacterial infections (pneumonia, pyomyositis)

and/or Performance scale 3: bedridden < 50% of the day during the last month

Stage 4: º HIV wasting syndrome.

º *Pneumocystis carinii* pneumonia

º Toxoplasmosis of the brain

º Cryptosporidiosis with diarrhoea, for more than 1 month

º Cryptococcosis, extrapulmonary

º Cytomegalovirus (CMV) disease of an organ other than liver, spleen, lymph nodes

º Herpesvirus infection, mucocutaneous for more than 1 month, or visceral any duration

º Progressive multifocal leukoencephalopathy (PML)

º Any disseminated endemic fungal infection (e.g. histoplasmosis)

WHO case definitions for AIDS surveillance in adults and children where HIV testing facilities are not available

Adults

The case definition for AIDS is fulfilled if at least 2 major signs and at least 1 minor sign are present.

Major signs

º Weight loss > 10% of body weight

º Chronic diarrhoea for more than 1 month

º prolonged fever for more than 1 month

Minor signs

º Persistent cough for more than 1 month

º generalized pruritic dermatitis

º History of herpes zoster

º oropharyngeal candidiasis

º Chronic progressive or disseminated herpes simplex infection

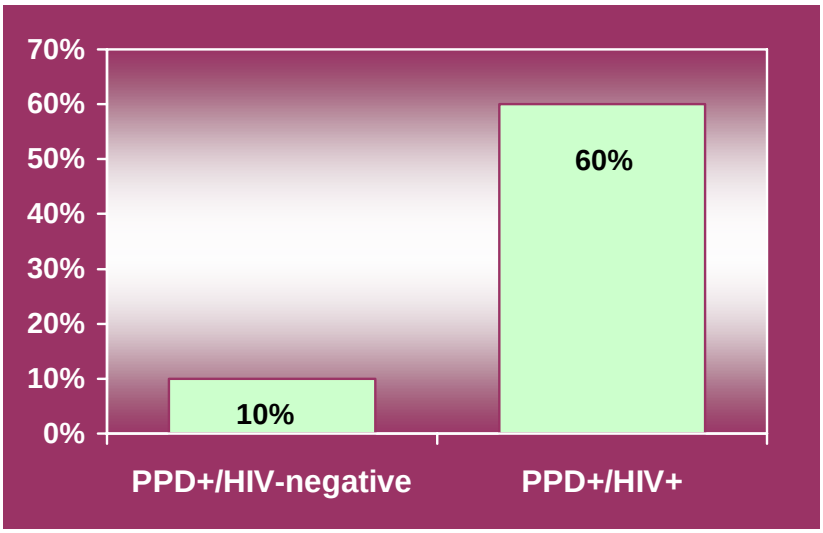
º generalized lymphadenopathy

The presence of either generalized Kaposi sarcoma or cryptococcal meningitis is sufficient for the case definition of AIDS.

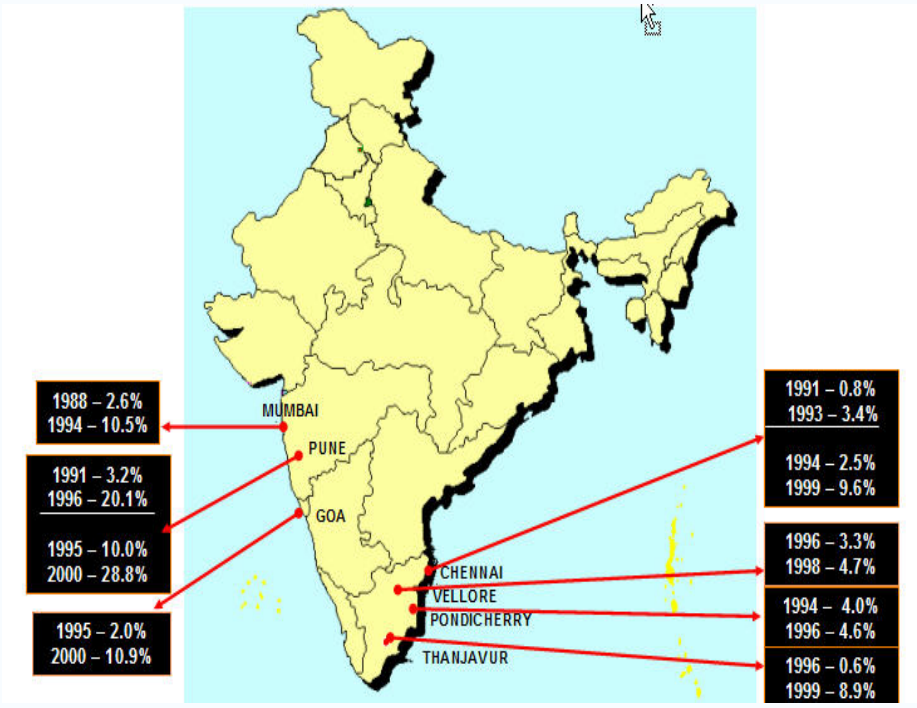
The advantages of this case definition are that it is simple to use and inexpensive. The disadvantages are its relatively low sensitivity and specificity. For example, HIV-negative TB cases could be counted as AIDS cases because of their similarity in clinical presentation.

PRACTICAL POINT

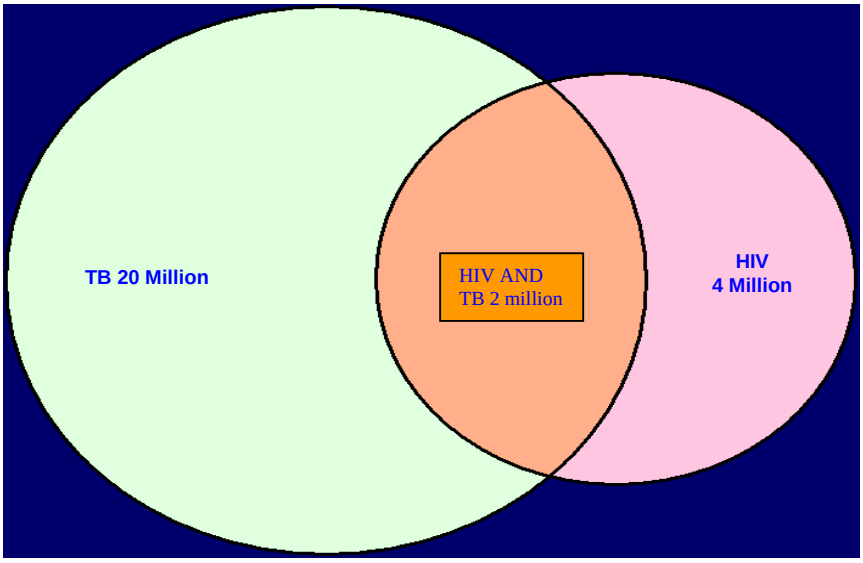
The term AIDS is used for epidemiological surveillance, not for clinical care. a *for patients with TB, persistent cough for more than 1 month should not be considered as a minor sign.*



RISK OF HIV IN TB PATIENTS



HIV AND TB COINFECTION IN SOUTH INDIA.



Picture showing estimated HIV and TB co infection in India

Features	Stage of HIV infection	
	Early	Late
Clinical Presentation	Often resembles Post-primary TB (Adult-type)	Often resembles Primary TB Extra pulmonary TB common
Sputum Smear Result	Often positive	Often negative
Chest X-ray Appearance	Often shows cavities	?Atypical presentation, often infiltrates ?Lower lung-field lesions, intra-thoracic lymph nodes & infrequent cavities

FEATURES AND CLINICAL PRESENTATION IN RELATION TO STAGE OF HIV INFECTION

Tuberculosis in HIV infection:

HIV has had a substantial effect on the incidence, clinical manifestations, treatment, and outcome of TB. Globally, HIV and TB are the 2 leading infectious causes of death.

People who are infected with HIV are at an increased risk of contracting tuberculosis. The WHO estimates that just over 20 million people are currently infected with HIV and of these 6 million are co-infected with *Mycobacterium tuberculosis* so Tuberculosis remains an important problem in patients with human immunodeficiency virus (HIV) infection.

Co infection with these pathogens can be particularly devastating, especially in the developing world, where the burden of disease is high and access to effective therapy is low.

Among infections associated with HIV, tuberculosis (TB) is unique in that it may be transmitted to immunocompetent persons via the respiratory route, is easily treatable once identified, may occur in early-stage HIV disease, and is preventable with drug therapy.

However, multi drug resistance is a potentially serious problem, even though its incidence has declined because of the use of directly observed therapy and other improved practices.

TB is a major opportunistic infection in HIV-infected patients, often representing their AIDS-defining illness and the first indication of immunodeficiency. Epidemiology, clinical manifestations, and management of TB are altered in HIV-infected patients.

Impact of HIV on TB

HIV is the most significant risk factor for progression from sub clinical infection with *Mycobacterium tuberculosis* to active TB [3,4].

However, when a person is dually infected with HIV and *M. tuberculosis*, the risk of developing TB significantly increases from 10% in a life time to 5%–15% per year[5-8]. HIV-infected persons are at markedly increased risk for primary or reactivation tuberculosis[9, 10] and for second episodes of tuberculosis from exogenous reinfection.[11] The lifetime risk for progressing to active TB among HIV-negative persons latently infected with *M. tuberculosis* is estimated at 10%. In contrast, among HIV-infected persons, the risk for progressing to active disease is approximately 10% *per year*,[12] and the immediate risk for progressive primary disease after recent infection with *M. tuberculosis* approaches 40%.[13] This interaction between TB and HIV accounts for much of the recent global resurgence in TB. Of note, however, HIV infection does not increase the infectiousness of persons with active TB.[14] The introduction of potent combination antiretroviral therapy in the developed world, which has

dramatically decreased the risk for opportunistic infections and death among HIV-infected persons, has also decreased the risk for developing active TB[15] and the risk for death among HIV-infected persons who develop active TB[16].

Epidemiology

The frequency with which HIV and Mycobacterium tuberculosis infection occur together is determined by the epidemiology of each disease in a given population. Highest rates are found in the homeless, injecting drug users, and recent immigrants and refugees[17].

The incidence of TB in HIV-infected persons is more than 100 times that of the general population. In untreated HIV-infected persons who have a positive tuberculin skin test, the risk of active TB is about 8% per year [18].

Nosocomial transmission of TB from HIV-infected patients to healthcare workers has been reported [19].

One of the most threatening features of TB in HIV-infected patients has been the spread of multi drug-resistant (MDR) organisms [20]. MDR TB is defined as disease that is resistant to at least two drugs (INH and Rifampicin). Its incidence has declined dramatically in recent years with more rapid case

identification, improved isolation practices, use of early empirical therapy with drugs directed against MDR strains [21], and use of directly observed therapy [22]

Pathogenesis

Tuberculosis can develop through progression of recently acquired infection (primary disease), reactivation of latent infection, or exogenous reinfection.

Infection with M tuberculosis can occur when an individual exposed to an infectious case of tuberculosis inhales particles (<5 µm in size) containing the tubercle bacilli.[23] If the bacilli reach the pulmonary alveoli, they may be ingested by alveolar macrophages, the first line of defense against M tuberculosis. Surviving tubercle bacilli multiply within the macrophage and eventually undergo hematogenous spread to other areas of the body.

Once infection does occur, however, the risk of rapid progression is much greater among persons with HIV infection, because HIV impairs the host's ability to contain new tuberculous infection.

Immunocompetent individuals infected with M tuberculosis have approximately a 10% lifetime risk of developing tuberculosis, [24] with half of the risk occurring in the first 1-2 years after infection.

CD4 cell-mediated immunity and macrophage function are essential in the control of M tuberculosis infection. During primary infection of an immunocompetent host, cell-mediated immunity usually develops and arrests

progression of disease. About 5% of patients whose primary infection is controlled have reactivation years to decades later. In another 5% of patients, infection is not contained, and primary pulmonary, extra pulmonary or disseminated TB can occur.

Susceptibility to tuberculosis is related to the pattern of cytokines produced by T lymphocytes. CD4+ lymphocytes, which produce interferon-γ, are central to antimycobacterial immune defenses, and fatal mycobacterial disease develops in children who lack the interferon-γ receptor.[25] In contrast to CD4+ lymphocytes, CD8+ lymphocytes, which produce interleukin-4 and interleukin-10, do not contribute to antimycobacterial immunity.[26] When peripheral-blood lymphocytes from HIV-infected patients with tuberculosis are exposed to *Mycobacterium tuberculosis* in vitro, they produce less interferon-γ but similar amounts of interleukin-4 and interleukin-10, as compared with lymphocytes from HIV-negative patients with tuberculosis.[27] These findings suggest that the reduced CD4+ response in HIV-infected patients contributes to their susceptibility to tuberculosis.

The hallmark of HIV infection is progressive deterioration and depletion of CD4 cells, coupled with defects in macrophage and monocyte function [28]. There is evidence that the immune response in patients with TB might enhance HIV viral replication and accelerate the natural progression of HIV infection [29].

The risk of TB developing in an HIV-infected patient who is latently co-infected with M tuberculosis approaches 10% per year, as opposed to a 10% lifetime risk in an immunocompetent host [30]. Patients with more advanced HIV infection (CD4 count, <200 cells/mm3) who are newly infected with M.tuberculosis may lack the ability to contain the primary infection, which can progress rapidly and is fatal if not treated. Infection with M tuberculosis in an immunocompetent person is thought to confer significant protective immunity against exogenous reinfection.[24] However, reinfection has been reported in HIV-seronegative[31,32] and -seropositive individuals,[33-37] although its incidence is not known

Tuberculosis and the Course of HIV Infection

Exposure of alveolar macrophages and lymphocytes from HIV-infected patients to *M. tuberculosis* in vitro up-regulates retroviral replication.[38,39]

TB has been associated with a 5- to 160-fold increase in HIV viral replication, which may decrease after successful TB treatment.[40]

Pleural fluid from patients with tuberculosis increases HIV replication in activated lymphocytes,[41] and in HIV-infected patients with pulmonary tuberculosis, the concentrations of retroviral RNA in bronchoalveolar-lavage fluid are highest in areas of tuberculous involvement.[42] *M. tuberculosis*

probably increases HIV replication by inducing macrophages to produce tumor necrosis factor-α, interleukin-1, and interleukin-6.[41,42]

Clinical studies have shown the detrimental effects of tuberculosis on the course of HIV infection. The risk of death in HIV-infected patients with tuberculosis was reported to be twice that in HIV-infected patients without tuberculosis, independently of the CD4 cell count.[43] The high mortality rate among patients with tuberculosis appeared to be due to progressive HIV infection rather than tuberculosis. The degree of immunosuppression is the most important predictor of survival in HIV-infected patients with tuberculosis, since negative tuberculin skin tests, prior opportunistic infections, and low CD4 cell counts are associated with increased mortality.[44,45]

Clinical presentation

Unlike other opportunistic infections, TB can occur in persons with early-stage HIV infection (CD4 count, >300 cells/mm3). Clinical presentation of TB in such patients is similar to that in healthy hosts with reactivation disease [46]. Patients are less likely to present with extrapulmonary disease at this stage of HIV infection. Because of the increased virulence in immunocompetent hosts of M tuberculosis compared with other opportunistic pathogens (e.g., Pneumocystis jiroveci), tuberculosis can occur early in the course of HIV infection. In several studies of HIV-infected patients with pulmonary

tuberculosis, the median CD4 T-cell count was >300 cells/mm3. (38) However, in patients with primarily extrapulmonary involvement or disseminated disease, the CD4 T-cell count may be much lower. For example, two studies in African patients with disseminated disease found the median CD4 T-cell count to be <80 cells/mm3.[47] A prospective study in the United States,[48] found the median CD4 T-cell count to be 144 cells/mm3 (range 2-543) in HIV-infected patients with all forms

of tuberculosis. Although tuberculosis can be a relatively early manifestation of HIV-1 infection, it is important to note that the risk of developing tuberculosis, and of disseminated infection, increases as the CD4 T-cell count decreases.

Typical symptoms include fever, weight loss, productive cough of several weeks' duration, and hemoptysis. Chest radiographs demonstrate the presence of focal infiltrates and/or cavitation involving the upper lobes.

In patients with advanced HIV disease, TB may present atypically and extrapulmonary TB is more common. Disseminated disease with involvement of bone marrow, bone, urinary and gastrointestinal tracts, liver, regional lymph nodes, and the central nervous system is common [30, 46].

Radiographic Findings

The chest radiograph is the cornerstone of diagnosis for pulmonary tuberculosis. Upper lobe infiltrates and cavities are the typical findings in reactivation tuberculosis, whereas intrathoracic lymphadenopathy and lower

lobe disease are seen in primary tuberculosis. In HIV-infected persons with higher CD4 T-cell counts (e.g., >200 cells/mm3) the radiographic pattern tends to be one of reactivation disease with upper lobe infiltrates with or without cavities. [49] In HIV-infected persons who have a greater degree of immunosuppression (e.g., CD4 T-cell count <200 cells/mm3), a pattern of primary disease with intrathoracic lymphadenopathy and lower lobe infiltrates is seen (Figure 2 and Figure 3). As chest radiographs may appear normal in 7-14% of cases, a high index of suspicion must be maintained in evaluating an HIV-infected patient with symptoms suggestive of tuberculosis. [50,51] .The finding of low-density lymph nodes with peripheral enhancement on a contrast-enhanced chest computed tomography (CT) scan is highly predictive of tuberculosis.

Chest radiographs may be normal or show evidence of perihilar or mediastinal lymphadenopathy without parenchymal lung involvement. Radiographs and clinical presentation may mimic community-acquired pneumonia or Pneumocystis carinii pneumonia. Cavitation is unusual at this stage of advanced immunosuppression, and infiltrates more often are diffuse or interstitial. Mycobacterial blood cultures may yield M tuberculosis in one third of patients with advanced HIV immunosuppression [52] a severely immunocompromised person presenting with TB may not show cavitation and may have only mild interstitial infiltrates. Pneumonia, lung tumors, and fungal

masses may also occur at the site of previously healed TB or granulomatous lesions.

Testing for HIV Infection in Patients with Tuberculosis

All patients with tuberculosis should be tested for HIV co infection because of the potential benefits of an early diagnosis of HIV infection.[53]

Selective HIV testing in patients with tuberculosis is unwise, because health care providers often fail to identify risk factors for HIV related to heterosexual transmission.[54] Even when patients with tuberculosis are questioned about risk factors for HIV infection, up to 5 percent of those who report no risk factors are infected with HIV.[54]

Diagnosis

In patients with TB and HIV infection, special consideration is required in assessing results of tuberculin skin test and acid-fast bacillus smear and culture.

Tuberculin skin test

HIV infection causes depression of cell-mediated immunity, which can reduce the sensitivity and reliability of the tuberculin skin test. Only 30% to 50% of HIV-infected patients who are co infected with M tuberculosis have a

positive result on the tuberculin skin test [46]. Although a positive result increases the likelihood of TB, a negative result does not exclude the diagnosis.

Therefore, diagnostic evaluation for TB should be undertaken in all patients who have clinical features compatible with TB, regardless of the results of the tuberculin skin test. Several cohort studies have demonstrated a high incidence of active tuberculosis among HIV-infected individuals with positive tuberculin skin test results.

There are recent reports of restoration of delayed hypersensitivity on skin testing, including tuberculin skin testing in HIV-infected patients who begin highly active antiretroviral therapy. This reaction reflects restoration of the anti-M tuberculosis cell-mediated immune response, a phenomenon that usually occurs within the first month of therapy [55].

Acid-fast bacillus smear and culture

In HIV-infected patients with pulmonary TB, cultures are positive in about 90% of cases and sputum smears are positive in about 50% to 70%--numbers that are similar to those seen in immunocompetent adults with reactivation TB [56].

Polymerase chain reactions and gene probes are approved for rapid identification of M tuberculosis in sputum smears that are positive for acid-fast bacilli. These rapid tests are more sensitive than traditional staining methods but are not as sensitive as culture. Smears from extrapulmonary sites (e.g., bone marrow, lymph nodes) are often negative for acid-fast bacilli. However, the sensitivity of culture approaches 90%, depending on the number of samples tested [57].

Bacteriologic Examinations

All patients suspected of having pulmonary tuberculosis should have 3 sputum specimens obtained on 3 consecutive days, and these specimens should be examined for AFB and cultured for mycobacteria. AFB identified on smear is not diagnostic of tuberculosis, as the acid-fast stain detects mycobacteria other than M tuberculosis, including M avium-intracellulare complex or M kansasii. However, until identification is confirmed, empiric therapy for tuberculosis should be initiated if the sputum smear is positive for AFB. The rate of AFB smear positivity has varied from 31% to 89% in HIV-positive patients. [58] In general, the rate of smear positivity correlates with the extent of radiographic disease. For example, patients with cavitary lesions due to active tuberculosis will almost always have positive smears, whereas a negative smear in a patient with minimal disease on chest radiograph would not be unusual, and

would not rule out active tuberculosis. However, in HIV-infected patients positive smears may be seen with relatively little radiographic involvement.

When expectorated sputum specimens are AFB smear-negative, further evaluation may be indicated. Bronchoscopy with bronchoalveolar lavage and transbronchial biopsy may be useful in the evaluation of an abnormal chest radiograph when sputum smears are negative. In this setting, a rapid diagnosis of presumptive tuberculosis, based on histology and AFB smear of specimens obtained by bronchoscopy, can be made in 30-40% of individuals, which is similar to the yield of bronchoscopy in HIV-negative cases with smear-negative pulmonary tuberculosis. [59].

Positive cultures for M tuberculosis provide a definitive diagnosis of tuberculosis. Approximately 15% of reported tuberculosis cases are culture negative, but these data are not available for HIV-infected cases. However, at San Francisco General Hospital, culture-negative tuberculosis in HIV-infected patients is seldom observed. (This perceived increase in sensitivity might be due in part to the increased use of diagnostic bronchoscopy in HIV-positive cases of suspected tuberculosis.) Unfortunately, culture results may not be available for 2-6 weeks, creating a need for more rapid diagnostic techniques.

Nucleic acid amplification (NAA) tests detect nucleic acid sequences unique to organisms in the M tuberculosis complex, allowing for a rapid

diagnosis. Two NAA tests, the Amplified Mycobacterium Tuberculosis Direct Test (MTD; Gen-Probe) and the Amplicor Mycobacterium Tuberculosis Test (Amplicor; Roche) have been approved by the U.S. Food and Drug Administration (FDA) for use in respiratory specimens in patients who have not previously been treated for tuberculosis. The MTD test is approved for use in smear-positive or smear-negative samples, whereas Amplicor is only approved for use with smear-positive samples.

A negative NAA test does not rule out the diagnosis of active tuberculosis, and antituberculous therapy and further diagnostic workup are needed if sufficient clinical suspicion for tuberculosis exists. The predictive value of NAA testing will vary depending on the sensitivity and specificity of the test in the local laboratory, as well as on the prevalence of M tuberculosis and other mycobacteria. Moreover, NAA testing does not provide information on drug resistance. NAA tests are an important addition to our armamentarium of diagnostic tools, but they do not replace AFB smear, culture, or, more importantly, clinical judgment.

Diagnosis of Latent Tuberculosis Infection

Screening for latent tuberculosis infection (LTBI) is an essential step in controlling the spread of tuberculosis. Screening for LTBI is recommended in persons at risk for recent infection and in those groups with increased risk of progression to active disease once infected, including HIV-infected persons.

The tuberculin skin test (Mantoux method) is currently the only method available for identifying LTBI. Routine annual tuberculin skin testing is recommended in HIV-infected individuals.

A reaction of >=5 mm induration is considered positive for HIV-infected patients and persons with other forms of severe immunosuppression, persons who are close contacts of infectious cases, and persons with abnormal chest radiographs consistent with tuberculosis.[60]. Use of the 5-mm cutoff is supported by a prospective study in the United States demonstrating that the risk of tuberculosis was significantly higher in HIV-infected persons with tuberculin skin test reactions >=5 mm of induration than in those who have a reaction <5 mm.[48]

It is important to keep in mind that a negative tuberculin skin test does not exclude infection or active disease. Testing with tuberculin purified protein derivative is dependent on the presence of an intact cell-mediated immune response. In the setting of HIV infection, reduced cell-mediated immunity can lead to decreased delayed-type hypersensitivity (DTH) responsiveness, resulting in False-negative skin tests. In a multicenter study in the United States, the prevalence of a positive tuberculin skin test (>=5 mm) was shown to decrease with decreasing CD4 T-cell counts.[61]

Persons who are at risk for tuberculous infection (e.g., injection drug users, individuals who are institutionalized or from high-prevalence regions)

should have a chest radiograph performed even if the tuberculin skin test is negative, particularly if their CD4 T-cell count is low. Annual chest radiographs should be considered in this high-risk group.

Application of multiple skin test antigens (e.g., Candida, mumps, tetanus toxoid, etc.), referred to as anergy testing, has been used to assess cell-mediated immune function and to distinguish true-negative from false-negative tuberculin skin test results. In 1991, the CDC recommended that anergy testing be performed in conjunction with tuberculin skin testing in HIV-infected persons based on the premise that anergic HIV-infected individuals at high risk for tuberculosis infection would benefit from treatment with INH. [62] In 1997, the CDC revised its recommendations and no longer recommends anergy testing while screening for M tuberculosis infection in HIV-infected persons. [63] The revised recommendation is based on the following points. First, there are no standardized guidelines for performing anergy skin testing. The appropriate number of control antigens to administer or the appropriate cut-off for interpreting a test as positive is not known. Second, the response to skin testing with control antigens as well as with tuberculin can vary over time. Several studies have demonstrated that HIV-1-seropositive individuals can regain DTH responsiveness with time. [64, 65, 66] In a multicenter study, Chin and colleagues[66] reported that 31% of anergic HIV-1-seropositive patients responded to DTH testing 1 year later. The only factor associated with regaining DTH

responsiveness was the CD4 T-cell count: the higher the CD4 count, the more likely the individual was to regain DTH responsiveness. Finally, treatment of LTBI in anergic HIV-infected persons has not been demonstrated to be beneficial.[67, 68]

In some individuals with tuberculous infection, DTH responsiveness may decrease with time. A second tuberculin skin test, applied weeks to months after the first, can "boost" the DTH response resulting in a positive skin test reaction. Such responses are considered true evidence of tuberculous infection. In a multicenter study in the United States, only 2.7% of HIV-1-seropositive patients "boosted" the tuberculin reaction with a second tuberculin skin test, despite relatively high demographic risk of tuberculous infection.[69] However, a study in Uganda found that 17 (29%) of 58 HIV-1-infected subjects responded to a second tuberculin skin test.[70]

Natural history

Although the immune response to M tuberculosis is important in controlling disease, immune activation may also be associated with increased HIV viral load and accelerated progression of HIV infection. A retrospective cohort study in the United States found that although only one patient in the group died of tuberculosis, HIV-infected patients with tuberculosis do not survive as long as HIV-infected controls without tuberculosis, even after controlling for baseline CD4 T-cell count. When tuberculin-positive HIV-

infected patients were given INH therapy in Haiti, they were less likely to develop AIDS and less likely to die than patients given placebo. [71] Thus, it is likely that tuberculosis acts to accelerate the clinical course of HIV infection.

Although increased viral replication is thought to play a role, the mechanisms by which tuberculosis accelerates progression of HIV disease are not known with certainty. High levels of tumor necrosis factor (TNF)-alpha, which are known to increase HIV replication in T-cell clones,[72] have been demonstrated in both HIV-1-seropositive and -seronegative tuberculosis cases.[73].

Moreover, Investigators have shown that M tuberculosis or purified protein derivative can also increase viral replication in infected T lymphocytes and monocytes.[74-76]A recent study demonstrated a 5- to 160-fold increase in viral replication during the acute phase of untreated tuberculosis.[72] The clinical significance of this increase in viral load is uncertain.

TREATMENT

STANDARD TREATMENT REGIMENS

Anti-TB therapy is equally effective in HIV-negative and HIV-positive patients. The weight of the evidence to date indicates that the rate of TB relapse after short-course (6-month rifamycin-based) therapy is similar for HIV-positive and HIV-negative patients, although this remains somewhat controversial.[77,78].

In general, then, the same treatment regimen may be used regardless of HIV status. The American Thoracic Society TB treatment guidelines (currently under revision) will likely include a recommendation to extend the duration of therapy to 9 months (regardless of HIV status) in persons who have both cavitary pulmonary disease on initial presentation and positive-sputum cultures after 2 months of treatment. These changes are based on results of a recent TB-treatment study conducted by the CDC, in which HIV-negative adults with pulmonary disease who met these criteria had a relapse rate of >20% -- far higher than the clinically acceptable relapse rate of <5%.[79]

In TB-endemic areas, recurrent TB after completion of a course of therapy is more likely to be due to exogenous reinfection than to relapse.[80.] Compared with HIV-negative TB patients, co infected patients have a higher risk for recurrent TB, but this is due to reinfection rather than relapse.[81] In a study conducted in Haiti, HIV-infected persons who completed a course of TB therapy were less likely to develop recurrent TB if they received a 12-month post-treatment course of isoniazid, compared with persons who received placebo.[82] However, such practice has been implemented neither in developing countries (due to insufficient infrastructure) nor in developed countries (due to lower TB incidence rates and lower rates of exogenous reinfection).

PHARMACOKINETIC INTERACTIONS

A central aspect of TB treatment in HIV-infected patients is the pharmacokinetic interactions between rifamycins (e.g., rifampin and rifabutin) and PIs and NNRTIs. Although these interactions do not preclude the concomitant use of potent antiretroviral therapy and anti-TB therapy, clinicians must be aware of these interactions and adjust dosages accordingly. Although large studies of the effectiveness of rifabutin-based regimens in co infected patients concomitantly receiving antiretroviral therapy are underway, the results will not be available for 1 to 2 years. However, 2 small studies have demonstrated that rifabutin-based regimens are well tolerated and effective in such patients.[83], [84]

DIRECTLY OBSERVED THERAPY

Self-administered TB therapy has been compared with directly observed therapy in very few well designed, randomized, controlled studies; however, the available data indicate that directly observed therapy is associated with decreased rates of TB incidence and drug resistance[85] and increased rates of sputum conversion and therapy completion.[86] Among HIV-infected patients, directly observed therapy has been associated with improved survival.[87] Because of these benefits, directly observed TB therapy is recommended by the American Thoracic Society, the CDC, and the WHO.[88], [89]

The regimen of DOTS is as shown below:

Category of Treatment	Type of patient	Regimen	Sputum Examination
CAT-I	New sputum smear positive Seriously ill sputum-negative Seriously -ill-EP	2 H3R3Z3E3/ 4 H3R3	0 2 4 6 3 5 7 MONTHS
CAT- II	Sputum smear + Relapse, Failure ,Treatment after Default	3 H3R3Z3E3S3/ 1 H3R3Z3E3/ 5 H3R3E3.	0 3 5 8 4 6 9
CAT-III	Sputum negative not seriously ill ,EP not seriously ill	2 H3R3Z3/ 4 H3R3	0 2 6

Abbreviations:

H- INH, R- Rifampicin, Z- Pyrazinamide, E- Ethambutol, S-Streptomycin.

HIV AND PARADOXICAL WORSENING OF TB

Paradoxical worsening of TB is the development of new signs or symptoms of TB disease or the exacerbation of existing manifestations of TB in patients receiving appropriate anti-TB therapy. Diagnosis of paradoxical worsening requires that other possible explanations be excluded, such as treatment failure, drug resistance, poor compliance, malabsorption, adverse drug reactions, and lymphoma. Paradoxical worsening is thought to represent an improvement of the host's immune response to mycobacterial antigens during the course of treatment, leading to more intense inflammation at sites of TB disease.

The estimated incidence of paradoxical worsening of TB in HIV-infected patients ranges from 7% to 36%, which is higher than the rate seen in HIV-negative patients. In one hospital-based study, higher rates of paradoxical worsening in co infected patients were associated with the use of antiretroviral therapy.[90] In a retrospective study of HIV-infected patients receiving outpatient TB treatment, the incidence of paradoxical worsening was not associated with the use of potent combination antiretroviral therapy, but patients experiencing paradoxical worsening while on antiretroviral therapy had a more severe and prolonged course. Paradoxical worsening of TB in HIV-infected patients has been associated with the presence of concurrent pulmonary and extrapulmonary TB at the time of initial diagnosis.[91]

The course of paradoxical worsening can be brief or prolonged, with multiple recurrences and exacerbations. Corticosteroid treatment of severe episodes of paradoxical worsening has not been associated with progression of TB disease or failure of anti-TB therapy. Patients with less severe symptoms may obtain relief with nonsteroidal anti-inflammatory medications. Although antiretroviral therapy may be associated with the development or severity of paradoxical worsening, discontinuation of therapy is not generally recommended.

TREATMENT OF LATENT TB INFECTION

As noted above, the risk for progressing to active TB is high among HIV-seropositive persons infected with *M. tuberculosis*. Therefore, all HIV-infected persons with evidence of latent *M. tuberculosis* infection should receive treatment. See Table 1 for the indications for treatment of latent infection in HIV-infected persons and potential treatment regimens. In a study among HIV-infected persons with latent *M. tuberculosis* infection, 2 months of daily rifampin + pyrazinamide was as effective as 12 months of daily isoniazid in preventing active TB; both regimens were well tolerated.[92] A recent study found that combination short-course regimens had a more durable protective effect than did isoniazid alone.[93.] However, there have recently been 6 hepatotoxicity-associated deaths reported among persons taking daily rifampin + pyrazinamide.[94], [95] Although none of the 6 persons was HIV-positive, the

recommendations for the treatment of latent TB infection have been revised to state that this regimen should not be offered to patients with underlying liver disease or with prior isoniazid-associated hepatotoxicity. This regimen should be used with particular caution in patients concurrently taking other medications associated with liver injury and in those with a history of alcohol abuse. See Table 1 for recommendations for toxicity monitoring during treatment for latent TB infection.

The WHO recommends treating latent *M. tuberculosis* infection in HIV-infected persons in the developing world. However, implementation of this policy has been incomplete due to limited resources in these settings. This is particularly true in settings in which resources are insufficient to identify and treat all persons with active TB, which remains a higher priority.

WHO recommendations for the treatment of TB and HIV co infection with reference to CD-4 cell count.

CD 4 cell count	**Recommended regimen**	**Comments**
< 200 mm^3	Start TB treatment. Start ART as soon as TB treatment is tolerated (2 weeks to 2 months) EFV containing regimens.	Recommended ART EFV is contraindicated in pregnant or women of childbearing potential without effective contraception
200 to 350 mm^3	Start TB treatment. start one of the below regimens after initiation phase: EFV containing regimens or NVP containing regimens in case of Rifampicin free continuation phase TB treatment regimen.	Consider ART
> 350 mm^3	Start TB treatment.	Defer ART
CD 4 count not available	Start TB treatment.	Consider ART

Abbreviations:

EFV- efavirenz, NVP – nevirapine.

DISCUSSION

The age groups commonly affected by tuberculosis infection among the HIV seropositives range from 20 to 40 years. This corresponds to other studies, both foreign and Indian, like, ***S. Rajashekaran et al.*** [96] who reports that the most common age group affected was between 21 to 40. ***Maheshwari et al,*** [97] and ***Nirgudkar et al***, [98] have also recorded the highest incidence of HIV-TB co-infection in the third decade.

Among the 347 patients infected with HIV infection, sixty-nine was having TB co-infection. Out of these sixty-nine patients, 68.11% were males, 26.08% were females and 5.8% were children. This indicates that the Male: Female ratio is 2.5:1. The incidence of TB co-infection in children is alarmingly high and more efforts are needed to prevent the congenital HIV infection and also to screen the HIV cases periodically for Tuberculosis infection.

The prevalence of HIV is more in the fourth decade (45.37%). The average age of the population is 33.3 years. This indicates that the economically productive group of the population is at the greatest risk of tuberculosis HIV co-infection thereby causing heavy loss to the society at a large.

Agricultural laborers were more commonly affected with HIV TB co-infection when compared to others. This indicates that the problem is more common in the economically backward groups in which malnutrition; overcrowding, hi-risk sexual practices are seen.

Immune Reconstitution Syndrome was observed in one case that developed lower lobe infiltration after starting ART with the anti tuberculous therapy for pleural effusion. This shows the enhancement of cell-mediated immunity.

Miliary mottling, diffuse infiltration, hilar-adenopathy and non-cavitary lesions were common in severe immunosuppression, CD4+ counts < 100. Upper lobe lesions were more common in early immuno-suppression, which is similar to the reports of the previous studies.

Anergy to Tuberculin skin testing was noted in thirty-five out of the sixty-nine patients studied (50.72%). This correlates well with the earlier studies by ***Johnson et al.,*** [99] ***Huebner et al***., [100] and the ***Baltimore based study- Graham et al***., [101] ***Jones et al.,*** [102] ***Mukadi et al***., [103] which show an increased incidence of anergy in HIV infected and the AIDS patients.

Analysis of the clinical presentation showed the following findings,

Fever was the most common clinical presentation followed by loss of appetite and cough. This finding corresponds to that of the earlier

observations of ***Modilevsky et al***., [104] and the ***Bellevue hospital study***, both reported that fever and cough were the predominant symptoms in TB- HIV co-infection patients. The ***registry*** of AIDS patients at ***NACO*** also shows that fever, cough and weight loss as the commonest symptoms.

Symptom analysis	Our study	**Rajasekaran S et al, Beenasusheel and Pai et al,**	Modilevsky et al,	NACO Registry.
	Fever, cough and loss of appetite and weight are common symptoms.	Fever, cough with expectoration loss of appetite and weight- common symptoms.	Fever and cough are the most consistent symptoms	Fever and cough are the common symptoms.

The sputum positivity in our study shows that only 22 percent of the individuals are sputum positive. This correlates well with other studies as discussed below,

Sputum culture for Mycobacterium tuberculosis remains the gold standard for the diagnosis of Pulmonary TB. In resource-poor countries the diagnosis is heavily dependent on the sputum AFB smear. HIV infected patients have been reported to have a lower yield on AFB smears. ***Brindle ea al***., [105] observed that HIV positive patients excreted slightly fewer

organisms per milliliter of sputum than did HIV negative patients with culture confirmed TB. Positive smears were observed in 31 to 89% of patients. ***Klein et al***., [106] reported only21% of smear positive cases in HIV infected patients compared to 35% in HIV negative patients. ***Kramer*** [107] reported an increase in the yield of smears when repeated up to five times.

Our study	Rajasekaran et al	Brindle et al,	Klein et al,
Smear negativity-78.26%.	71 % sputum smear negativity	HIV patients excreted fewer organisms per ml; (31-89%)	21% smear positivity in HIV infected patients

The results of fiber optic bronchoscope derived samples for smear examination are variable. ***Miro et al*** [108] reported an increase in the yield of smears in broncho alveolar lavage specimen, though statistically insignificant. The results of ***Kennedy et al***, [109] ***Salzmann et al,*** [110] showed a

statistically significant increase in the yield of smears for AFB in broncho alveolar lavage specimens.

Smear positivity varied with the nature of X- ray lesion occurrence of which in turn depends on the immune status of the individual. ***Greenbaum et al*** reported 52% positive smears with cavitary disease and only 32% positives in local infiltrates. ***Barnes et al***, [111] found positive smears in 90% of patients with radiographic findings typical of adult reactivation and in 98% of patients with cavitary TB.

In our study, a CD 4+ cell count < 200 was observed in 45 out of the sixty-nine patients. In these patients, the predominant X-ray lesions were hilar adenopathy, lower lobe infiltrations, diffuse infiltrations and miliary mottling. This finding correlates well with the studies conducted in south Africa by ***Post FA Wood, R Pillay et al,***[112] in this study the lower zone infiltration and hilar adenopathy were common with lower CD4 + counts- mean value of 105. Upper lobe infiltration was common with higher CD 4+ counts- mean 389. Similar results were published by several studies like the one in ***NEJM Feb 4, 1999***. ***David Perlman et al*** [113] reported increased incidence of hilar adenopathy with advanced immuno-suppression.

In our study most of the patients fall under stage III of the WHO staging system (thirty five out of the sixty-nine patients- 50.72%)

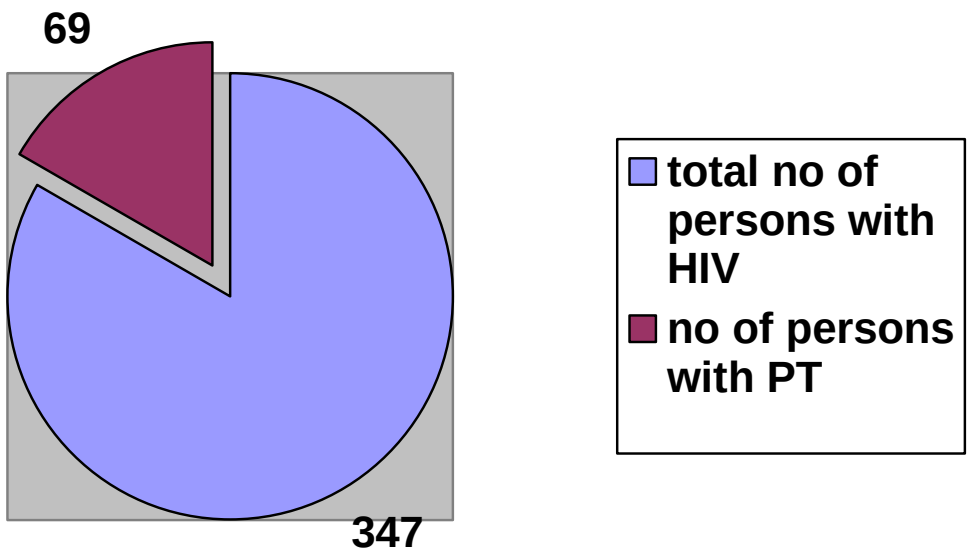
Pulmonary Tuberculosis infection is reported in stage III of the WHO guidelines.

CD 4+ cell count	Our study	Pillay Study	Perlman study
< 200	Hilar adenopathy, Lower lobe infiltrates and Diffuse infiltrations- common	Lower zone, Hilar adenopathy – common.	Hilar adenopathy – common.

RESULTS:

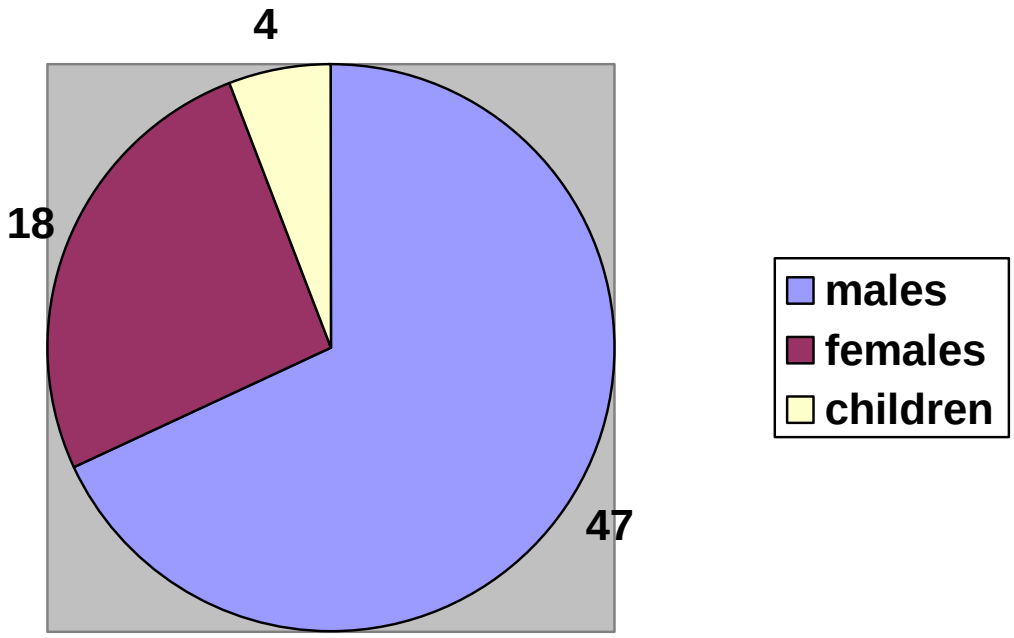
The study population was derived from the persons attending outpatient department at Thanjavur Medical College and the attached Raja Mirasudar Hospital. Out of the 347 confirmed cases of HIV infection 69 persons were found to be suffering from pulmonary tuberculosis, they formed the study population.

The prevalence of pulmonary tuberculosis in HIV was 69 out of 347 i.e. 19.88%



SEXWISE DISTRIBUTION:

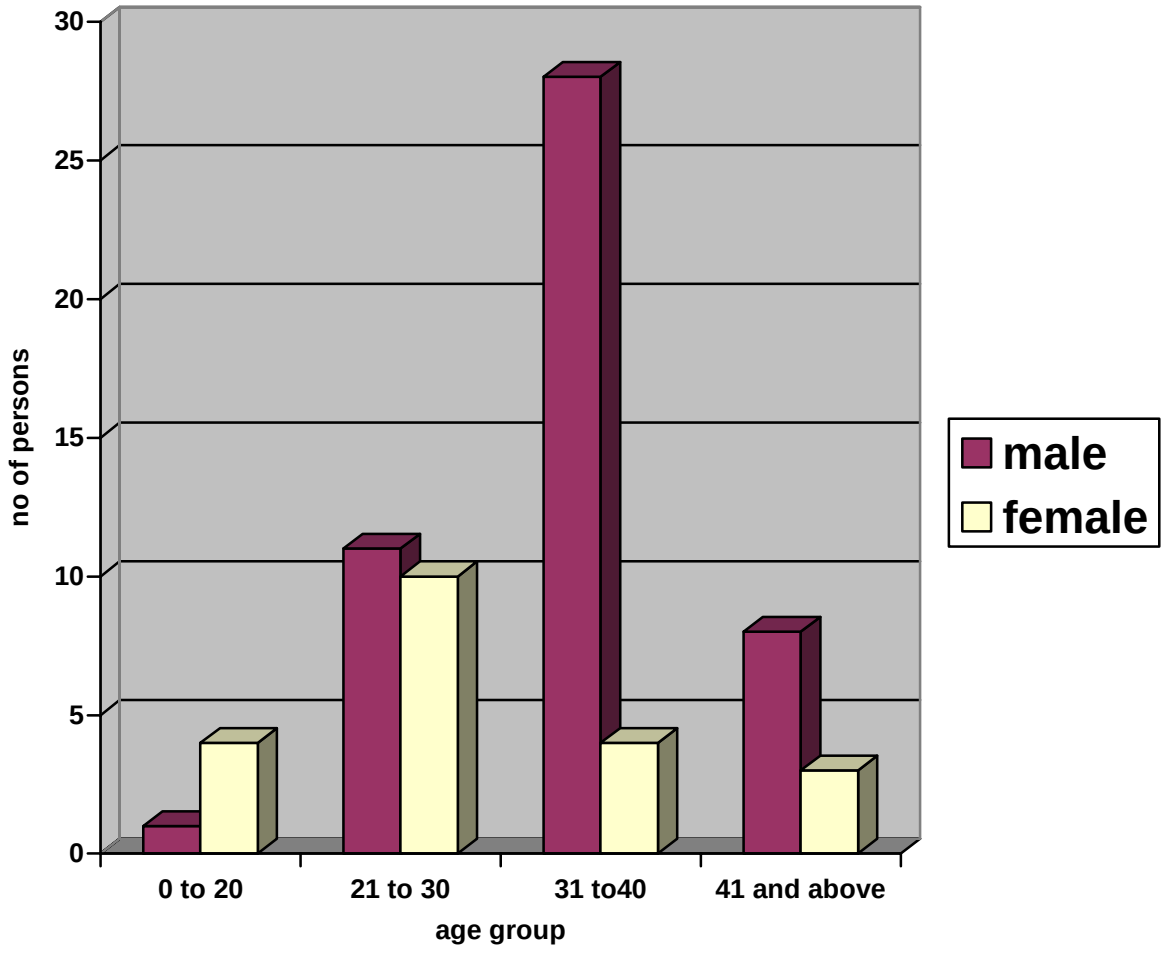
Out of the 69 patients with TB and HIV co infection 47(68%) were males 18(26%) were females and 4(6%) were children.



AGE:

The age wise distribution of cases was as follows:

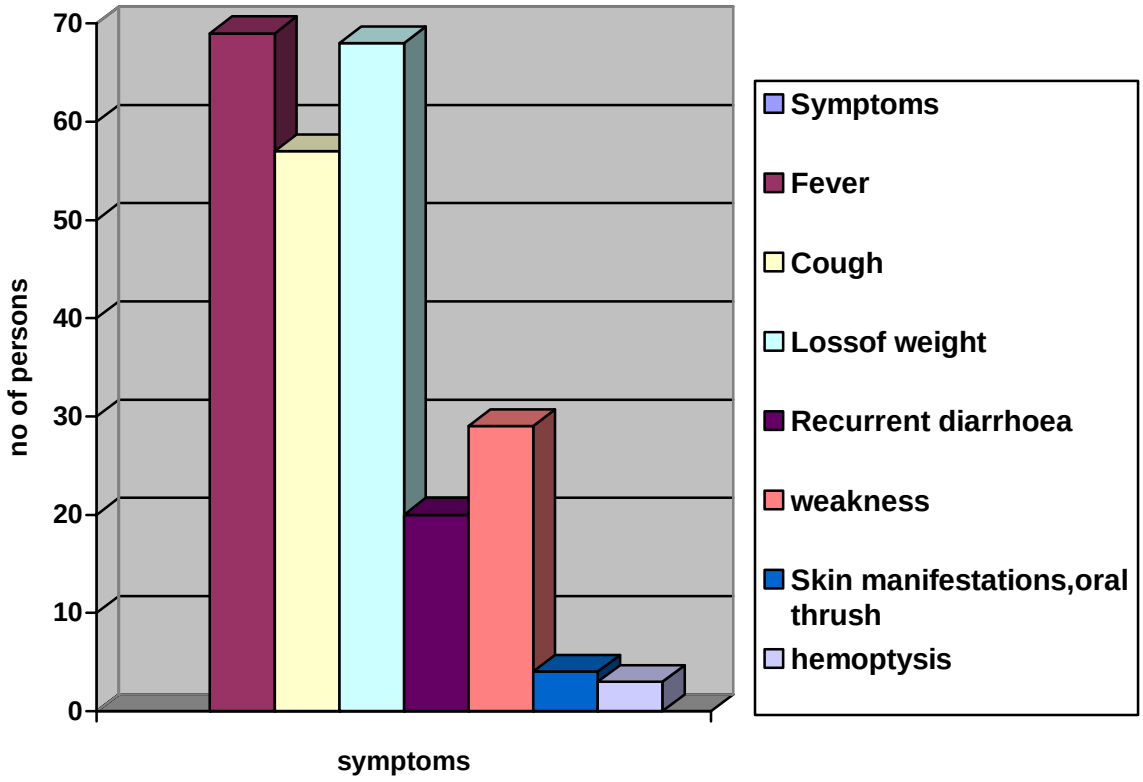
Age group	Male	Female
0to 20	1(1.4%)	4(5.8%)
21to 30	11(16%)	10(14.5%)
31 to 40	28(40.5%)	4(5.8%)
41 and above	8(11.5%)	3(4.3%)



SYMPTOMS:

The symptoms present in patients of the study group are as follows:

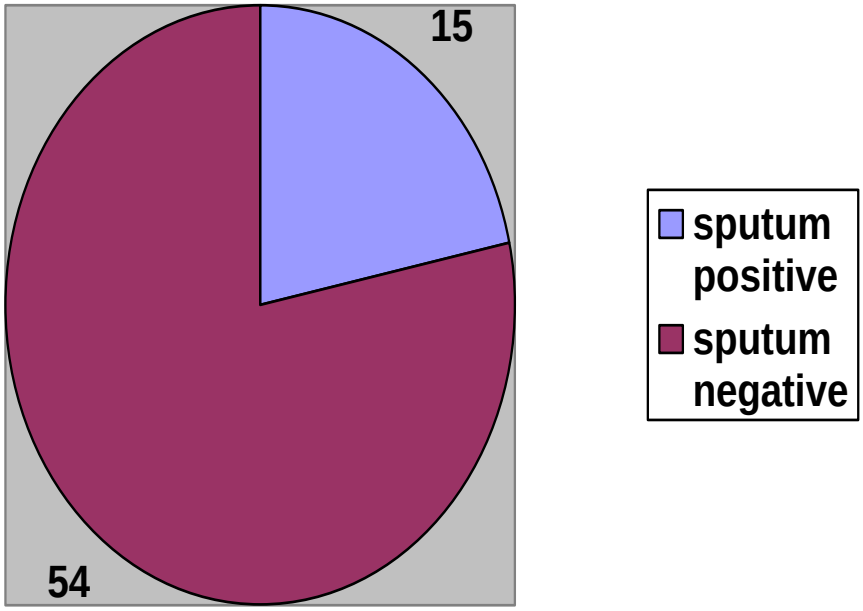
Symptoms	Number
Fever	69 (100%)
Cough	57 (82.6%)
Loss of weight	68 (98.5%)
Recurrent diarrhea	20 (29%)
Weakness	29 (42%)
Skin manifestations, oral thrush	4 (5.8%)
Hemoptysis	3 (4.3%)



SPUTUM POSITIVITY:

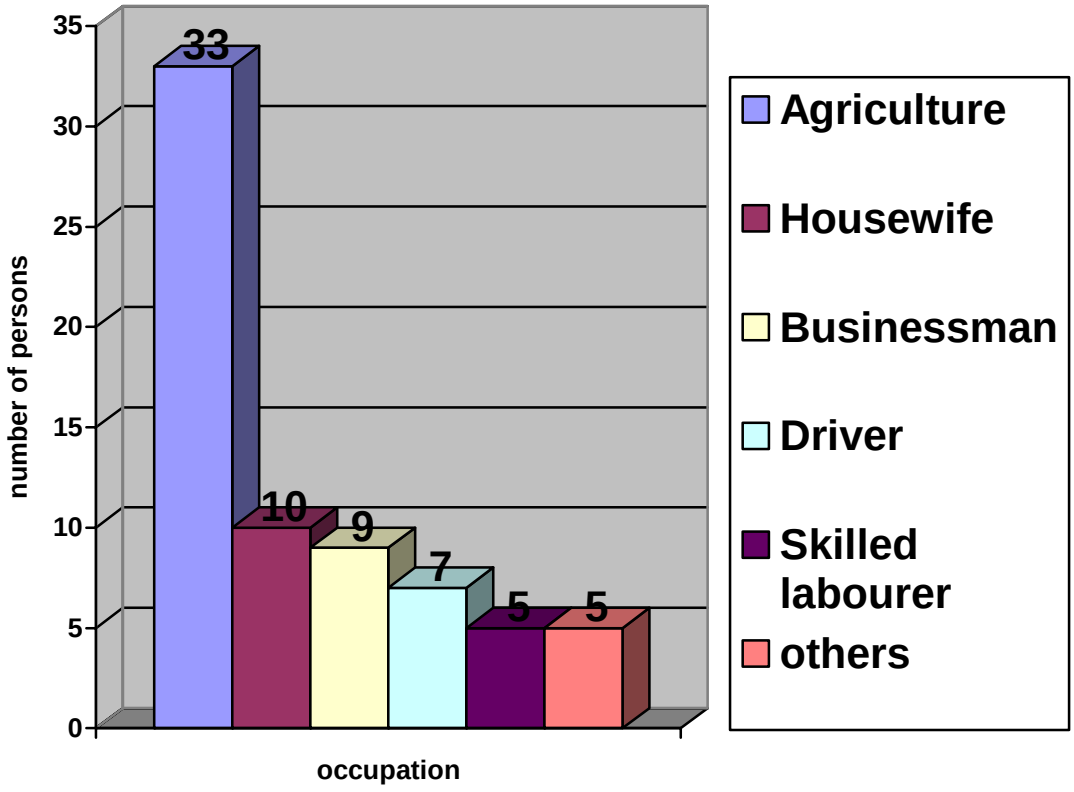
The result of 2 spot and one early morning sputum microscopic examination for acid-fast bacilli is as follows:

Positive 15(21.74%) negative 54(78.26%)



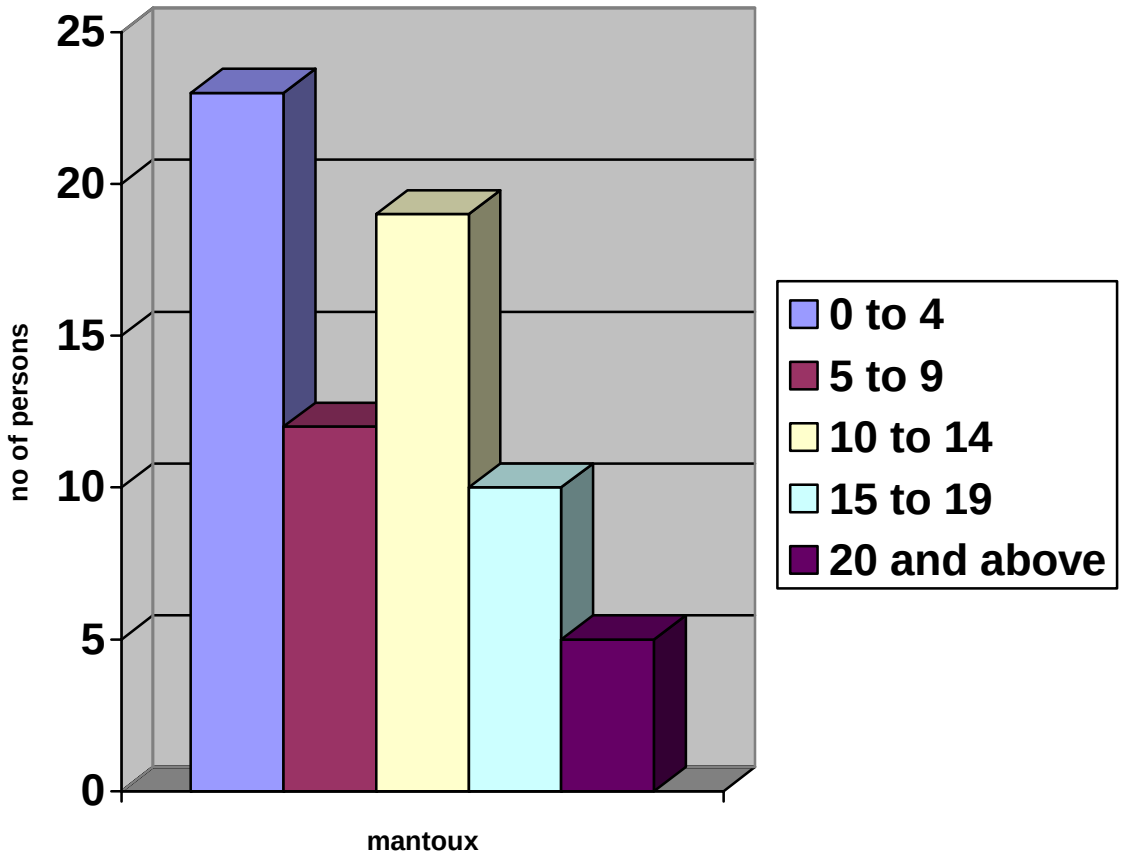
The occupation of patients is as follows:

Occupation	Number
Agriculture	33 (47.8%)
Housewife	10 (14.5%)
Businessman	9(13%)
Driver	7 (10%)
Skilled laborer	5 (7.2%)
Others	5 (7.2%)



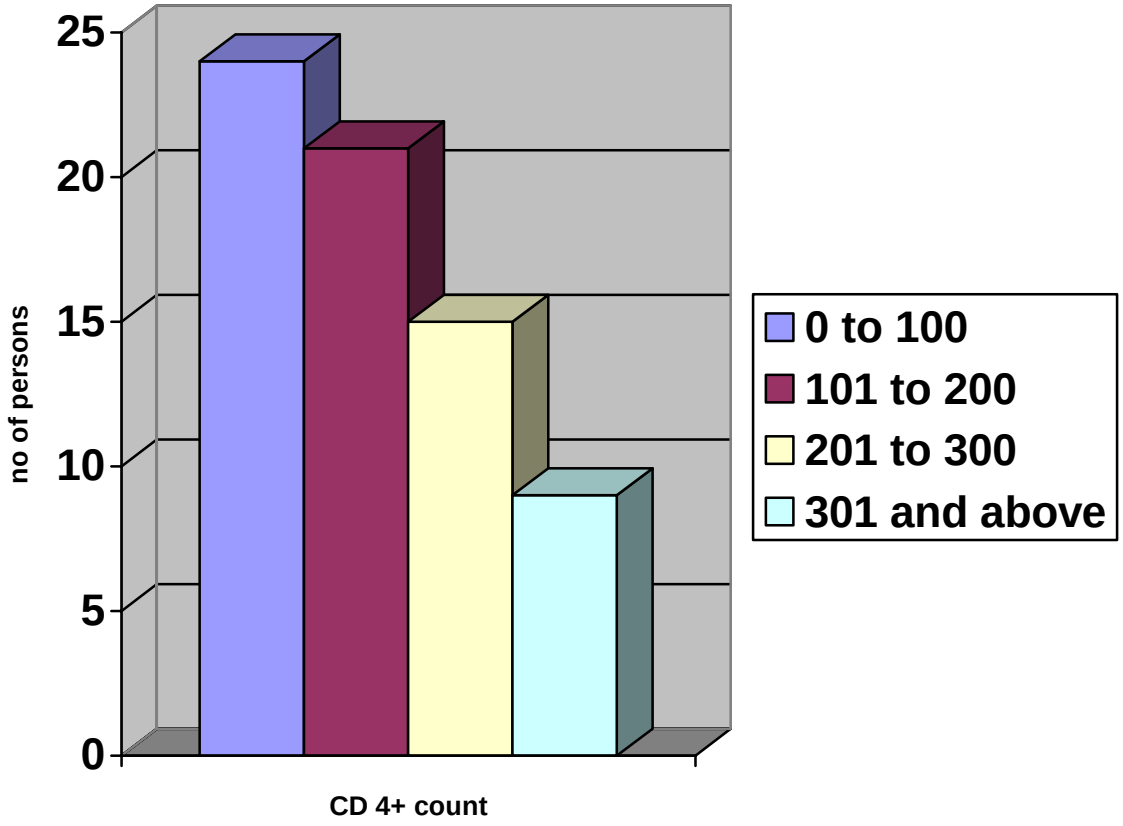
The **Mantoux test** results are as follows:

Mantoux reading (mm)	Number
0 to 4	23 (33.3%)
5 to 9	12 (17.4%)
10 to 14	19 (27.5%)
15 to 19	10 (14.5%)
20 and above	5 (7.2%)



The CD 4 cell count in patients was as follows:

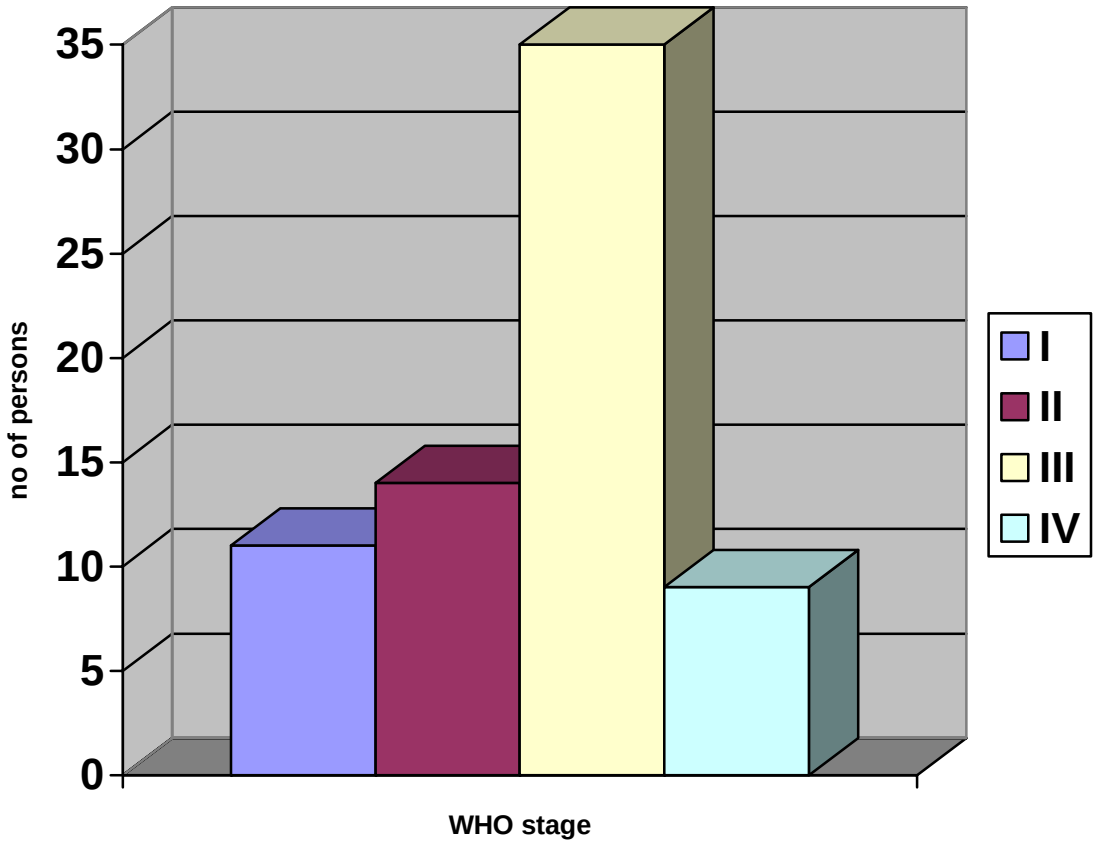
CD 4 count	Number
0 to 100	24 (34.8%)
101 to 200	21 (30.4%)
201 to 300	15 (21.7%)
301 and above	9 (13%)



WHO clinical staging:

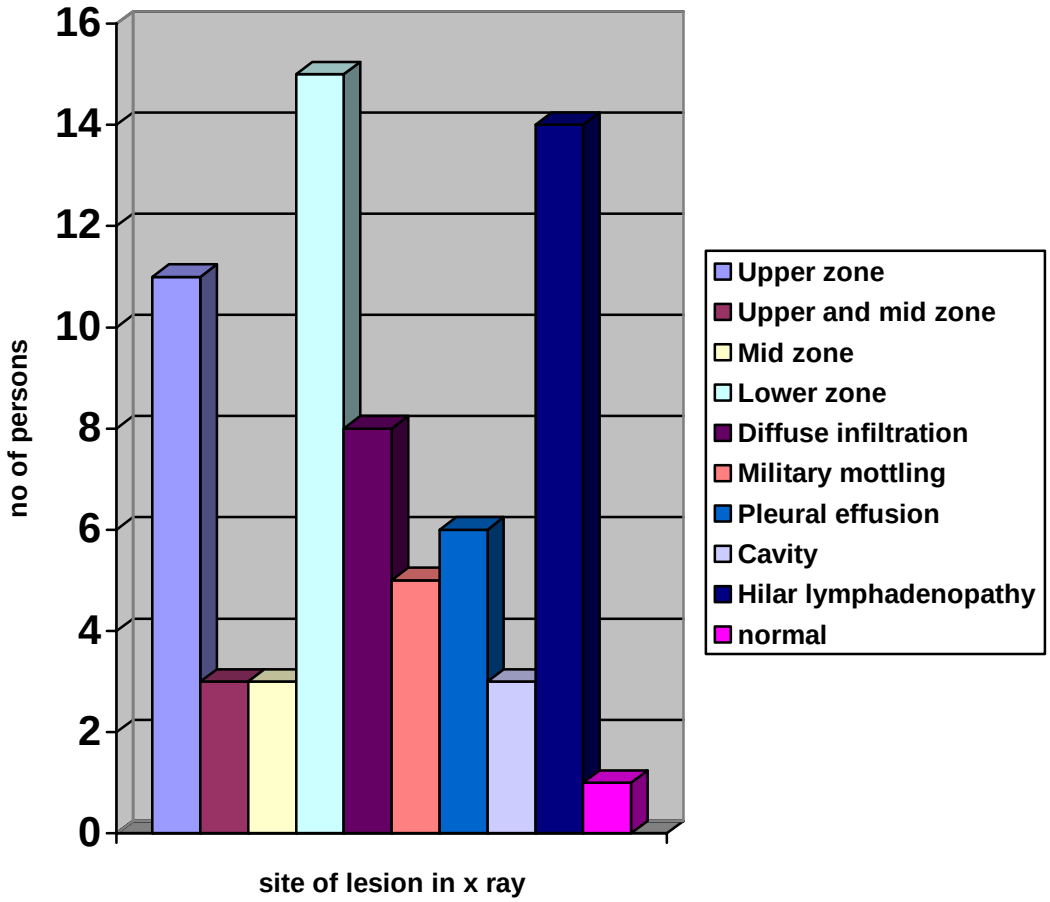
The patients' distribution according to the WHO clinical stage is as follows;

WHO stage	Number
I	11 (16%)
II	14 (20.3%)
III	35 (50.7%)
IV	9 (13%)



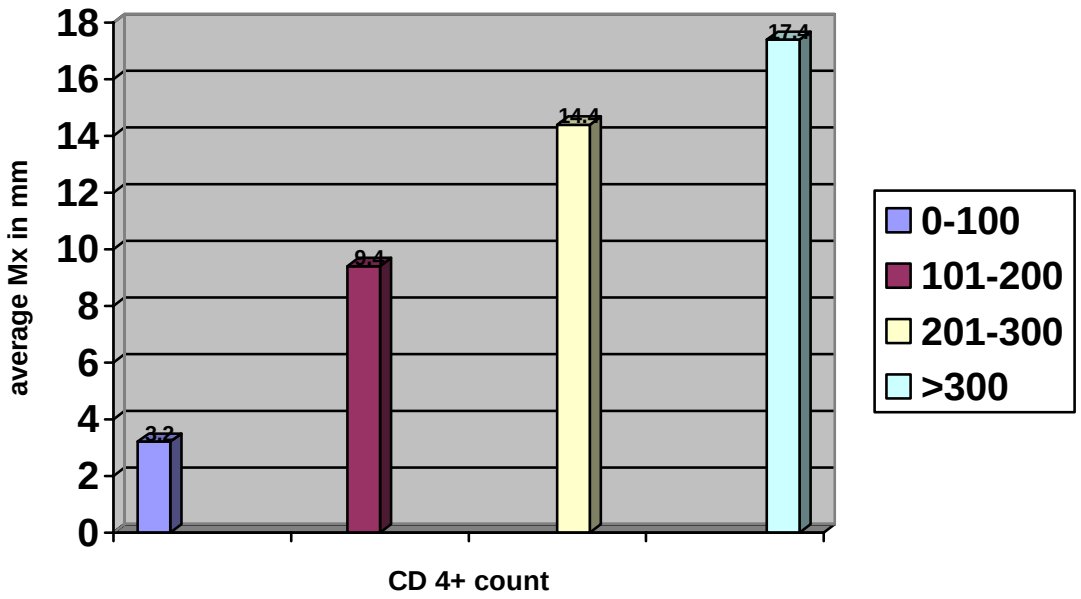
The distribution **of X ray lesions** in the study population is as follows:

Site of lesion	Number
Upper zone	11 (15.9%)
Upper and mid zone	3 (4.3%)
Mid zone	3 (4.3%)
Lower zone	15 (21.7%)
Diffuse infiltration	8 (11.6%)
Military mottling	5 (7.2%)
Pleural effusion	6 (8.7%)
Cavity	3 (4.3%)
Hilar lymphadenopathy	14 (20.2%)
Normal	1 (1.4%)



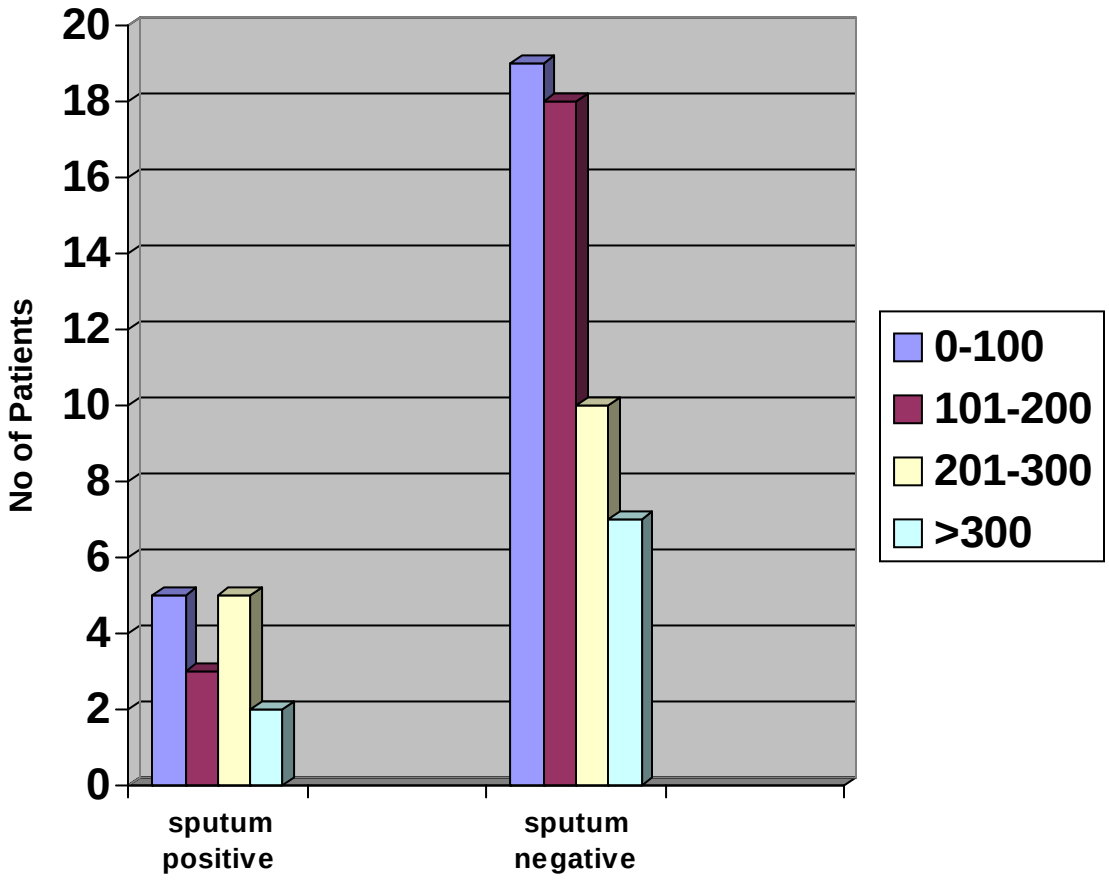
The average Mantoux in mm in relation to CD4+ cell counts is as follows,

CD 4 + COUNT	**AVERAGE MANTOUX READING** (in mm)
0 - 100	3.2
101- 200	9.4
201- 300	14.4
> 300	17.4



The Sputum AFB status in relation to the CD4+ cell counts is as follows,

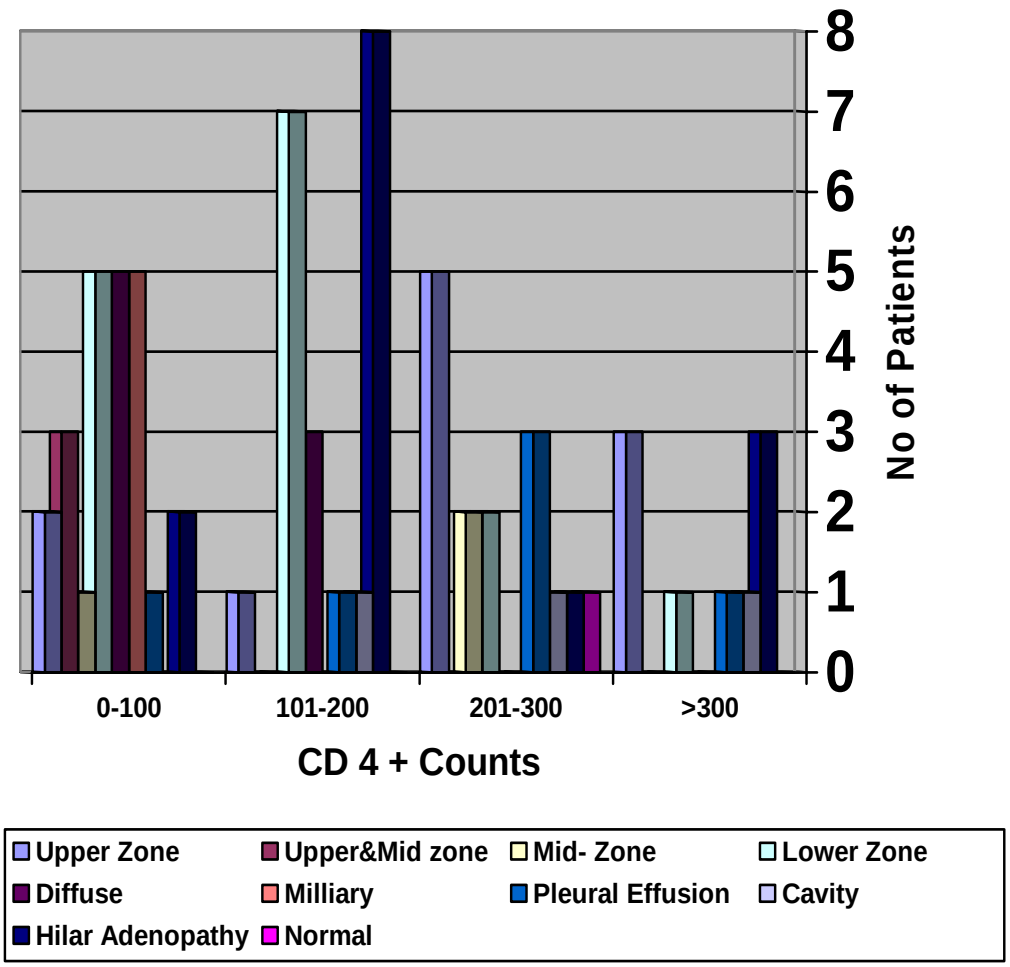
CD 4 + COUNT	SPUTUM POSITIVES	SPUTUM NEGATIVES
0 - 100	5 (7.2%)	19 (27.5%)
101- 200	3 (4.3%)	18 (26.1%)
201- 300	5(7.2%)	10 (14.5%)
> 300	2(2.9%)	7 (10.1%)



Chest X-ray findings observed in relation to the CD4 + cell counts is as follows,

CD4+ COUNT	UPP.Z	UPP-MID Z	MID.Z	LO.Z	DIFF	MIL	PL.EFF	CAV	HA	NOR
0-100	2	3	1	5	5	5	1	0	2	0
101-200	1	0	0	7	3	0	1	1	8	0
201-300	5	0	2	2	0	0	3	1	1	1
>300	3	0	0	1	0	0	1	1	3	0

UPP.Z: Upper Zone UPP-MID Z: Upper and middle Zone MID.Z: Middle Zone LO.Z: Lower Zone DIFF: Diffuse infiltrates MIL: Miliary Mottling PL.EFF: Pleural Effusion CAV: Cavity HA: Hilar Adenopathy NOR: Normal.



The most common side effect of drug therapy was gastritis. Minor skin rashes were observed after starting ART. One case of Immune Reconstitution Syndrome was observed.

CONCLUSION

Pulmonary Tuberculosis is a common opportunistic infection among the HIV seropositive individuals.

Pulmonary Tuberculosis occurs early in the HIV infection even before the CD 4+ count falls to very low levels.

Males are more commonly affected than females.

Agricultural workers and the low income group were commonly affected.

Fever, cough and loss of appetite and weight were the most common symptoms observed in HIV-TB co-infection.

Sputum negativity was more commonly seen in Pulmonary tuberculosis of HIV seropositive individuals.

Mantoux anergy was observed with lower CD 4+ counts.

Pattern of Primary Tuberculosis infection was seen in the X-ray of HIV seropositive individuals with TB co-infection in the lower CD 4+ count groups. A pattern of post-primary pulmonary tuberculosis was seen in the more immunocompetent group.

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